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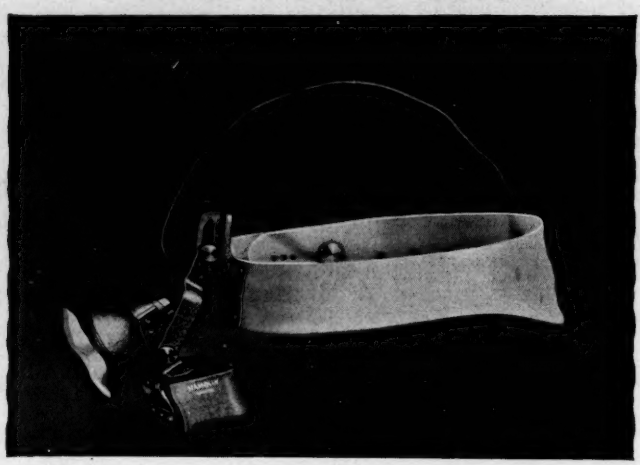

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COMMUNICATIONS

EFFECT OF DIENCEPHALIC STIMULATION UPON INTRA-OCULAR PRESSURE*

BY

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THERE is much clinical evidence to suggest that certain types of glaucoma are related to activity of the autonomic nervous system. This does not imply that the aetiology of glaucoma is necessarily bound up with autonomic dysfunction, nor deny the importance of factors such as anatomical closure of the angle or increased resistance to outflow of aqueous humour as a result of changes in the trabecular network or beyond. The acute attack of glaucoma following an emotional disturbance is perhaps the most frequently encountered example of this suggested relationship.

Whilst much work has been done on the chemistry of the aqueous humour and its outflow, relatively little has been done on the nervous mechanisms influencing intra-ocular pressure. With regard to the latter, attention has been directed mainly to the peripheral nervous system. It is known, for example, that stimulation of the cervical sympathetic trunk and fifth cranial nerves in cats and rabbits is accompanied by changes in intra-ocular pressure, whilst stimulation of the third and seventh cranial nerves affects the intra-ocular pressure only in so far as the muscles supplied by these nerves contract and press on the eye causing a temporary acute rise in pressure (Greaves and Perkins, 1952, 1953, 1956; Perkins, 1955, 1957).

In view of the known effects of stimulation of the peripheral nerves and the probable influence of autonomic factors on intra-ocular pressure, it has been suggested that higher vegetative centres may exert some control upon the pressure within the eye, and recent evidence supporting this view has been clearly summarized by Sir Stewart Duke-Elder in the 1957 Bowman Lecture.

Undoubtedly, further physiological investigation is necessary and only in the last few years have specific attempts been made to investigate changes in intra-ocular pressure resulting from stimulation of the central nervous system; in particular, the diencephalon has received most attention, as this part of the brain is known to influence many bodily functions. Such studies have been reported by Schmerl and Steinberg (1950), Nagai and others (1951), Weinstein (1954), von Sallmann and Lowenstein (1955), and Gloster

* Received for publication May 28, 1957.

and Greaves (1956). In the last paper we presented a preliminary report of our results which are now dealt with in greater detail.

Methods

Stereotaxic Apparatus.—The principles of stereotaxic technique are well known, but to satisfy the special requirements of our experiments, the apparatus was designed to give good access to the eyes of the animal and to provide fixation of the inferior orbital margin without pressure on the eye-ball.

The apparatus is illustrated in Figs 1(*a*) and 1(*b*); it is seen to consist of a heavy base-plate (B) with two vertical pillars (P, P) carrying adjustable ear-plugs (E, E); also a raised movable platform (D) with adjustable lugs to fix on the inferior orbital margins (M) and hard palate (N).

The electrode (C) is carried in a chuck and collet held in an arm (S) attached to a modified compound lathe-slide (L). The compound slide allows movement in two directions at right angles in a horizontal plane. The electrode can be moved vertically, movement in this direction being measured by a millimetre scale on the electrode chuck.

The whole arrangement allows free movement of the electrode, and the provision of millimetre scales enables the position of the electrode tip to be determined with reference to three planes at right angles to one another:

(1) a horizontal plane passing through the central points of the ear-plugs and the points of contact of the lugs (M) with the inferior orbital margins;
(2) a vertical plane passing through the centres of the ear-plugs;
(3) a vertical plane at right angles to (2) passing through the mid-line of the apparatus.

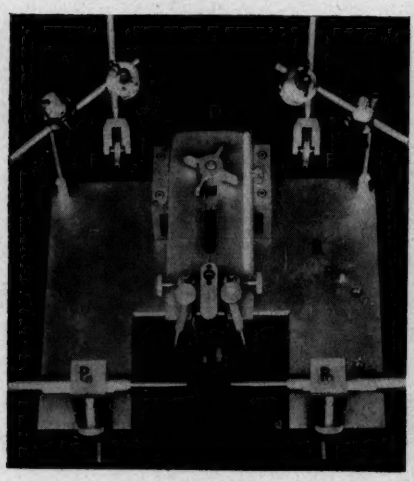


FIG. 1 (*a*).—Stereotaxic apparatus with electrode-carrier removed. For explanation of symbols see text.

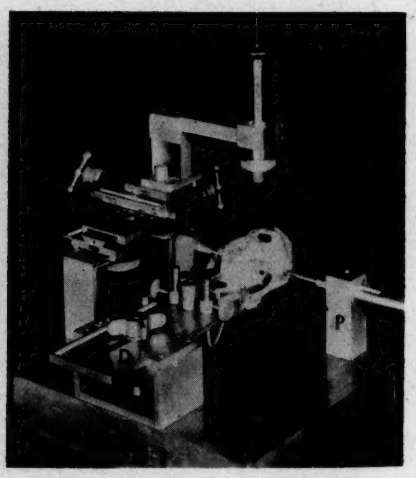


FIG. 1 (*b*).—Stereotaxic apparatus with electrode in carrier, skull positioned but nictitating membrane pulleys and their supports removed. For explanation of symbols see text.

It is pertinent at this stage to emphasize our nomenclature. All frontal planes are defined in millimetres in front of the vertical inter-aural plane, prefixed by the letter "A", thus A12, A9, etc. Measurements in a vertical direction were referred to the horizontal plane passing through the external auditory meatuses and the inferior orbital margins; we termed this the "zero horizontal" or "H" plane. Measurements to the right or left of the mid-line are given in millimetres prefixed by the letter "R" or "L" respectively. Thus a point in the brain referred to as "A12, H+7, R3" is 12 m. in front of the inter-aural plane, 7 m. above the horizontal plane, and 3 m. to the right of the mid-line.

Preparation of Animal.—Male cats weighing approximately 3 kg. were anaesthetized by intravenous injection of a 1 per cent. solution of chloralose (100 mg./kg.) after induction with ether. In some animals the trachea was cannulated to ensure a good airway throughout the experiment. The skull was exposed through a longitudinal incision in the scalp. Ear-plugs of suitable size were chosen and pushed firmly into the external auditory meatuses. The head was then mounted in the stereotaxic apparatus by means of the plugs and adjusted so that the sagittal suture coincided as closely as possible with the mid-line of the instrument. The inferior orbital margins were then secured by means of the lugs (M, M and N, N, Fig. 1). With the aid of a dental burr, holes were drilled in the skull in the positions required for the insertion of electrodes. In order to allow adequate inspection of the eyes, lateral canthotomies were performed and the upper eye-lids elevated slightly with sutures.

The intra-ocular pressures were recorded photographically using manometers connected directly to needles inserted in the eyes (Greaves and Perkins, 1952). The systemic blood pressure was similarly recorded from a cannula in the femoral artery. The movements of the nictitating membranes were recorded on the same film by means of threads running from the membranes (Fig. 2, overleaf) over pulleys (F, F, Fig. 1*a*) to levers on which small mirrors were mounted.

Stimulation

(*a*) *Electrode.*—Unipolar stimulation was used throughout, the cathode being in the brain, and the anode, a brass rod, in the rectum. The electrode itself was a 0·1-mm. diameter nickel wire inside a glass capillary tube of 0·125-mm. bore and 0·8-mm. external diameter. This type of electrode was chosen on account of its rigidity, reliability, and simplicity.

(*b*) *Stimulus.*—Square wave, direct current pulses of 1 msec. duration at a frequency of 30 c/s were provided by an electronic generator (Attree, 1950). These values were found suitable in a preliminary series of experiments in which maximal pupillary dilatation was obtained with the electrode in the lateral hypothalamus. With a resistance of 33,000 ohms in series with the electrode and the output of the generator set at 12 volts, measurements with an oscilloscope in several experiments showed that the current passing during stimulation was 0·2 ma. at a potential of 2·8 volts across the electrodes. The circuit and characteristics of the stimulus were unchanged throughout the series of experiments.

(*c*) *Introduction of Electrode.*—The electrode was lowered into the brain so that its tip lay 15 mm. above the "zero horizontal" plane, *i.e.* at H+15. 3 minutes later the stimulus was applied for 60 seconds. Subsequent stimulations, each of

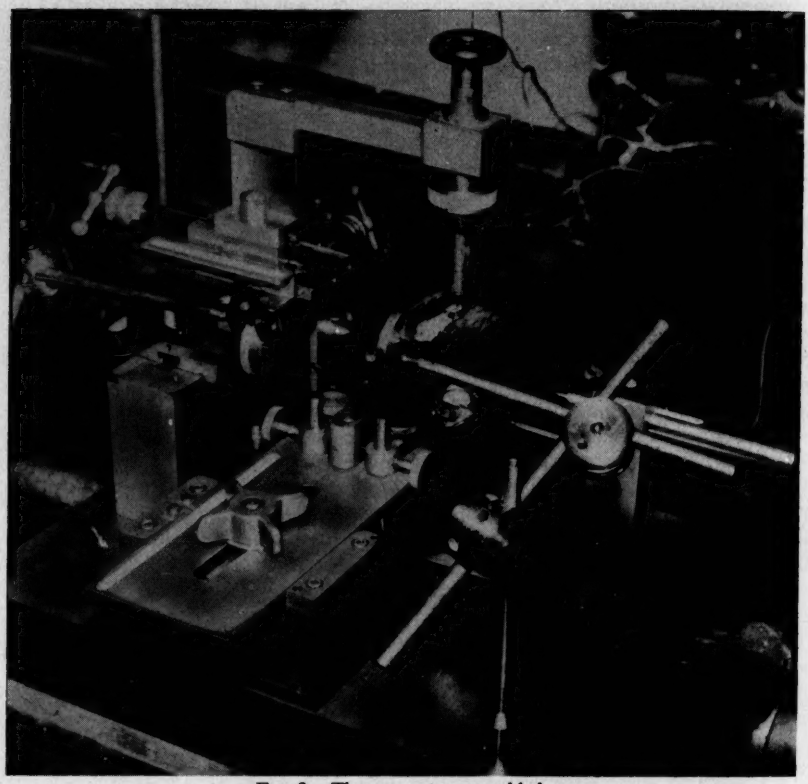


FIG. 2.—The apparatus assembled.

60 seconds' duration, were made at intervals of 5 minutes, the electrode being lowered 1 mm. between stimulations, the lowest position of the tip varying between H + 3 and H + 7 according to the frontal plane. The electrode was passed down two such tracks on each animal, one on each side of the midline, and generally separated by 7 mm. Only one stimulation was given for each position of the electrode tip.

During each stimulation, the changes in pupillary size were noted together with any ocular movement or muscular contraction in the region of the orbit.

Histology.—When stimulation had been completed, the electrode was withdrawn and six steel marker-needles inserted 7 mm. lateral to the mid-line in Plane 1, and 5 mm. in front of and 5 mm. behind the plane of the electrode tracks. After insertion of the marker-needles, the heart was excised and the head of the cat was elevated for a short time to exsanguinate the cerebral tissues. The brain was then removed and placed in formol-saline. After it had been embedded in paraffin, 10 μ sections were cut and stained with haematoxylin and eosin. Sufficient sections

were cut to ensure that the lowest point reached by the electrode tip could be recognized.

Assessment of Results.—The responses to each stimulation were entered on specially prepared tables, changes in blood pressure and intra-ocular pressure being recorded quantitatively. The *magnitude* of the change was judged only from that which occurred *during* stimulation. Movements of the nictitating membranes were considered to be of significance only when greater than 1 mm. on the tracing. Changes in pupillary size were recorded in the same table, together with observations on any contraction of facial musculature.

The results were then plotted on maps of frontal sections of the diencephalon, the maps being adapted from the atlas of Jasper and Ajmone-Marsan (1955). A separate map in each frontal plane was prepared for each of the following: pupillary reactions, blood pressure changes, nictitating membrane responses, and the correlation between changes in intra-ocular pressure and blood pressure. For convenience, the responses were plotted on one-half only of each map, irrespective of whether the electrode track lay to the right or left of the mid-line.

The positions of points within the brain from which the responses were obtained were mapped only after examination of the slides showing the electrode tracks, allowance being made for shrinkage of the brain-tissue during histological preparation.

Results

The results will now be presented under four headings:

(1) Pupillary responses.
(2) Nictitating membrane effects.
(3) Blood pressure changes.
(4) Intra-ocular pressure changes.

(1) Pupillary Responses.—Figs 3*a*, 3*b*, and 3*c* (overleaf) show diagrammatically the points from which pupillary changes were elicited in frontal planes A9, A12, and A15.

Only the responses of the pupil on the same side as the stimulating electrode are shown and, for the sake of simplicity, these ipsilateral responses have been plotted on one-half only of the maps, irrespective of whether the electrode was actually to the right or to the left of the mid-line. This seemed reasonable in view of the fact that the pupillary responses of the ipsilateral and contralateral eyes did not differ significantly in either magnitude or rate of response. It will be seen that, whilst these responses were obtained from widely scattered points in the diencephalon, the most marked effects were encountered in the posterior part of the hypothalamus. Only maps of planes A9, A12, and A15 are shown. Whereas the distribution of responses in planes A10 and A11 did not differ materially from those in A9 and A12, there were fewer points yielding pupillary dilatation in the more anterior regions of the diencephalon, *viz.* in planes A13 and A14.

The rate of response appeared to be dependent upon the position of the electrode tip. In the hypothalamus the response was rapid, dilatation commencing almost as soon as the stimulus was applied and reaching a maximum 10–15 seconds later; sometimes this maximum was maintained until the end of stimulation, but on other occasions it lasted for only about 30 seconds, after which a gradual decrease in pupillary size was observed during the remaining 20 seconds of stimulation. In the thalamus the pupillary responses were infrequent and small, and the average rate of response often appeared to be slower than that usually seen with hypothalamic stimulation.

Contractions of the pupil were seldom noted, but this was not surprising since under the conditions of our experiment the pupils were normally slits. The only points from which stimulation produced pupillary constriction were in the optic tract in plane A12, and from isolated points in A8. This last plane has not yet been examined by us in detail.

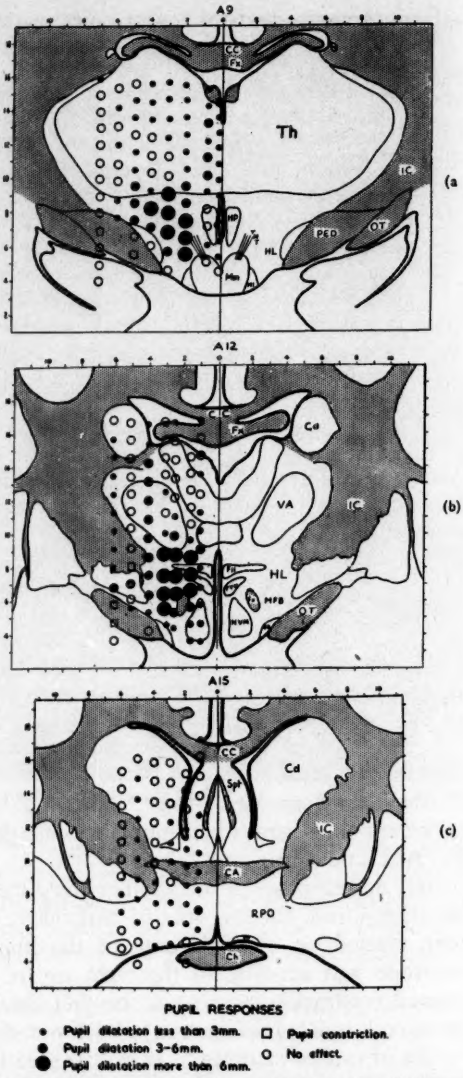


FIG. 3 (*a*), (*b*), (*c*).—Pupillary responses in frontal planes A9, A12, and A15. For explanation of lettered symbols see Appendix.

A second series of maps was prepared from the results of experiments in which the positions of stimulation had been found histologically to duplicate those used in the first series. Although the second group of maps is incomplete, there is considerable agreement between the two series.

(2) Nictitating Membrane Effects.—Nictitating membrane responses were not commonly observed (68 responses in 757 stimulations), and when elicited were small compared with the effect obtained by stimulation of the cervical sympathetic trunk. Both contractions and relaxations were recorded, but the latter were extremely small and less frequent. Ipsilateral effects occurred more frequently than contralateral effects.

With regard to contractions, we noted that the nictitating membrane tracing exhibited two types of movement:

(1) a fairly rapid rise followed by a slow return (*e.g.* as on Fig. 10);
(2) an abrupt rise at onset and an equally abrupt fall at the cessation of stimulation (*e.g.* as on Fig. 9).

After further examination of these tracings, we concluded that the former reflected smooth muscle activity whilst the latter suggested that striated muscle was in some way involved, possibly through attachments between the recti muscles and orbital smooth muscle.

The first type of effect was never accompanied by movement of the eyes and was sometimes bilateral, although the ipsilateral response was generally greater. This type of response was obtained from the hypothalamus in the frontal planes A11 and A12, mostly in the region of the anterior column of the fornix.

The second type of effect was always ipsilateral and was sometimes accompanied by movement of the eye on the same side. On one occasion, histological examination revealed that the electrode had passed through the ventral surface of the hypothalamus, the tip presumably being in the neighbourhood of the third cranial nerve. All other responses of this type were obtained when the electrode tip was in the extreme ventral part of the hypothalamus about 2–3 mm. from the mid-line.

(3) Blood Pressure Responses.—Since the intra-ocular pressure is known to be influenced by changes in systemic blood pressure, this latter was recorded continuously. A brief account will now be given of the changes in the blood pressure *per se*.

Simple rises and falls, and complex responses of the blood pressure were obtained from a wide area of the diencephalon, but, in contrast to the pupillary effects, these responses showed considerable variation from animal to animal. Thus, stimulation of a particular area within the diencephalon might be accompanied by a rise in blood pressure in one animal, whilst stimulation of the same area in another might result in a fall. There was some indication from the results that the type of response was partly dependent upon the general level of the blood pressure; in animals with a high initial blood pressure stimulation was frequently accompanied by a fall in blood pressure and *vice versa*.

The response usually started promptly at the commencement of stimulation

and sometimes persisted for a period after the stimulus was switched off or was succeeded by a temporary change in the opposite direction.

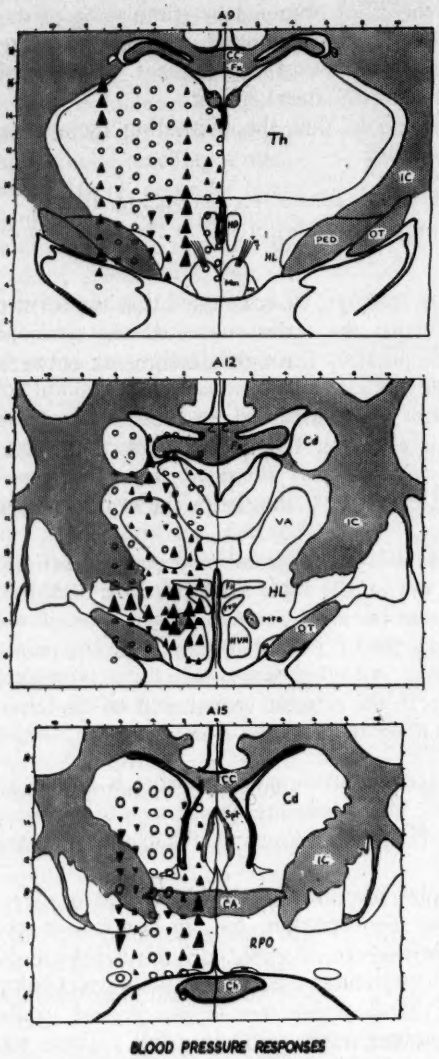


FIG. 4 (*a*), (*b*), (*c*).—Blood pressure responses in frontal planes A9, A12, and A15. For explanation of lettered symbols see Appendix.

With regard to localization, the maps (Figs 4*a*, 4*b*, and 4*c*) show that most responses were obtained from the hypothalamus, rises in blood pressure predominating in its medial part; this was noticeably so in planes A12 and A13. In the lateral hypothalamus, falls in blood pressure were not uncommon. Responses were also obtained from the thalamus, but these were relatively small.

(4) Intra-Ocular Pressure Effects

(*a*) *Types of Response.*—In the previous section we drew attention to the influence of the systemic blood pressure on intra-ocular pressure. It is of considerable importance therefore to take into account all such changes when analysing intra-ocular pressure responses, and the simultaneous recording of these effects allows this essential comparison to be made. For the purpose of this analysis, we have divided the responses into nine groups; the Table shows the incidence of the responses obtained in each group for both ipsilateral and contralateral eyes out of a total series of 745 stimulations. This Table has been compiled from two series of experiments, the second of which consists of duplications

of positions in the first series and is incomplete. The inclusion of the incomplete series does not alter materially the distribution of responses over the nine groups, since an analysis of the first complete series agreed with that presented for the combined results.

TABLE

PERCENTAGE INCIDENCE OF VARIOUS COMBINATIONS OF RESPONSES OF INTRA-OCULAR PRESSURE AND BLOOD PRESSURE IN 745 STIMULATIONS

Number of responses in each group is given in brackets

Blood Pressure	Intra-Ocular Pressure					
	Ipsilateral Eye			Contralateral Eye		
	Rise	No Change	Fall	Rise	No Change	Fall
Rise	17·0 (127)	17·4 (130)	2·6 (19)	16·5 (123)	19·5 (145)	1·2 (9)
No Change	7·9 (59)	44·4 (331)	0 (0)	6·0 (45)	46·0 (343)	0·1 (1)
Fall	3·5 (26)	6·2 (46)	0·9 (7)	3·2 (24)	6·3 (47)	1·1 (8)

In general, each type of response occurs with the same frequency in the two eyes. The occasions on which both intra-ocular pressure and blood pressure showed no change comprise almost half the total number of stimulations. Slightly more than half of the number of stimulations which were accompanied by intra-ocular pressure changes were also accompanied by changes in blood pressure in the same direction. The most interesting intra-ocular pressure changes were those which were independent of blood pressure changes, and these occurred in approximately 15 per cent. of stimulations in the ipsilateral eye and in 10 per cent. in the contralateral eye, an independent rise being much more common than a fall.

Figs 5 to 11 (overleaf) constitute a series of tracings illustrating the various effects already described.

(*b*) *Localization of Points from which Independent Changes in Intra-Ocular Pressure were Obtained.*—In Figs 12(*a*)–12(*g*) the responses of the intra-ocular pressure which were independent of blood pressure changes are correlated with the points stimulated in the diencephalon for frontal planes A9 to A15 inclusive. Only the responses of the ipsilateral eye are shown. The effects in the contralateral eye, though similar, were less numerous, but the distribution of points from which they were obtained was essentially the same as for the ipsilateral eye.

It should be noted that independent falls in intra-ocular pressure resulted from stimulation in the immediate vicinity of the anterior column of the fornix, whilst independent rises were obtained from a much wider area of the diencephalon.

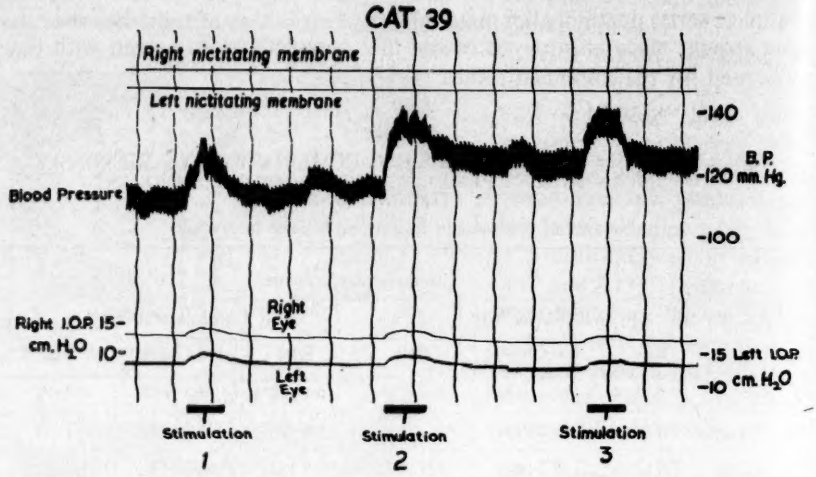


Fig. 5.—Tracing showing rises in intra-ocular pressure combined with blood pressure changes in the same direction. Interval between vertical lines represents 60 sec.

Localization: A14, R2 (see Fig. 12*f*)

Stimulation 1: H+7
Stimulation 2: H+6
Stimulation 3: H+5

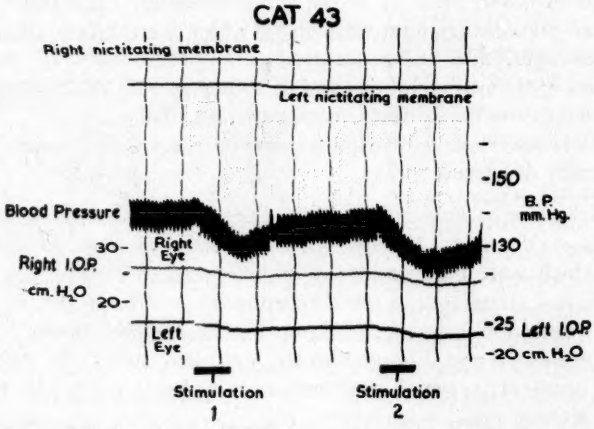


FIG. 6.—Tracing showing falls in intra-ocular pressure combined with falls in blood pressure. Interval between vertical lines represents 60 sec.

Localization: A15, R2 (see Fig. 12*g*)

Stimulation 1: H+14
Stimulation 2: H+13

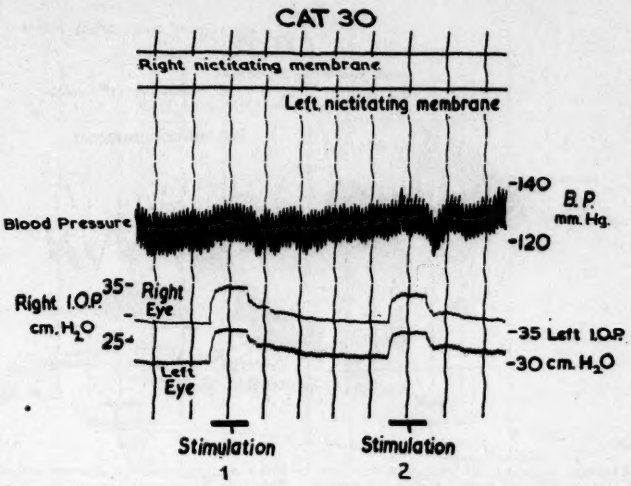


FIG. 7.—Tracing showing marked independent rises in intra-ocular pressure without blood pressure responses. Note abrupt rise and fall in intra-ocular pressure response. Interval between vertical lines represents 60 sec.

Localization: A9, R3 (see Fig. 12*a*)
Stimulation 1: H+12
Stimulation 2: H+11

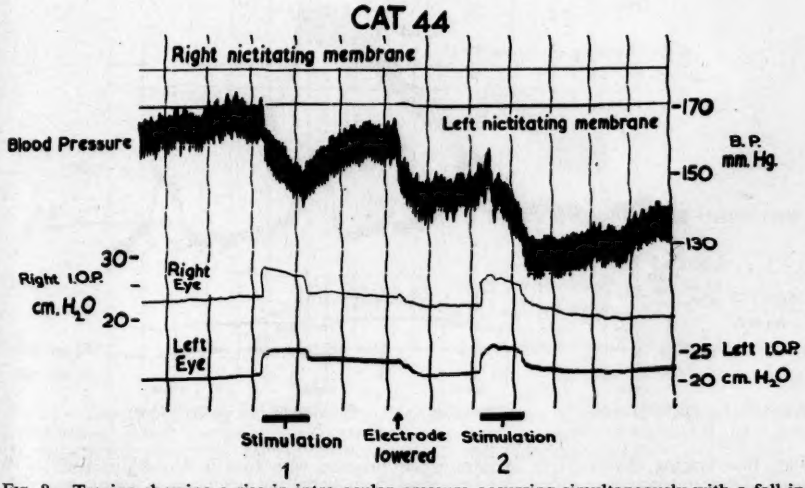


FIG. 8.—Tracing showing a rise in intra-ocular pressure occurring simultaneously with a fall in blood pressure. Again the intra-ocular pressure change is abrupt. Lowering the electrode has resulted in a fall in blood pressure and a *fall* in intra-ocular pressure. Interval between vertical lines represents 60 sec.

Localization: A9, L4 (see Fig. 12*a*)
Stimulation 1: H+8
Stimulation 2: H+7

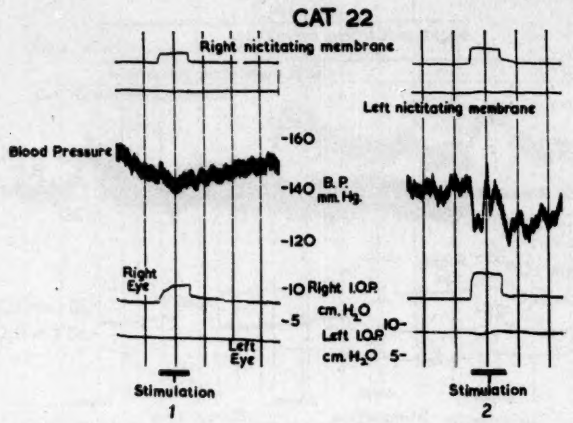


FIG. 9.—Tracings showing an independent rise in intra-ocular pressure accompanied by a contraction of the ipsilateral nictitating membrane. The *abrupt* movement of the latter suggests striated muscle activity. See text. Interval between vertical lines represents 60 sec.

Localization: A11, R4 (see Fig. 12*c*)
Stimulation 1: H + $6\frac{1}{2}$
Stimulation 2: H + $5\frac{1}{2}$

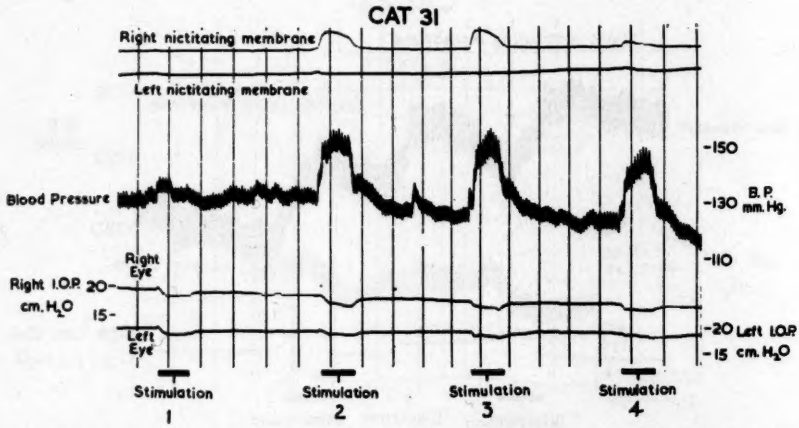


FIG. 10.—Tracing showing falls in intra-ocular pressure with rises in blood pressure. Note marked rises in blood pressure and contractions of right nictitating membrane in Stimulations 2–4. Interval between vertical lines represents 60 sec.

Localization: A12, R1·5 (see Fig. 12*d*)
Stimulation 1: H + $8\frac{1}{2}$ Medial hypothalamus
Stimulation 2: H + $7\frac{1}{2}$ Approximately level of fornix
Stimulation 3: H + $6\frac{1}{2}$
Stimulation 4: H + $5\frac{1}{2}$

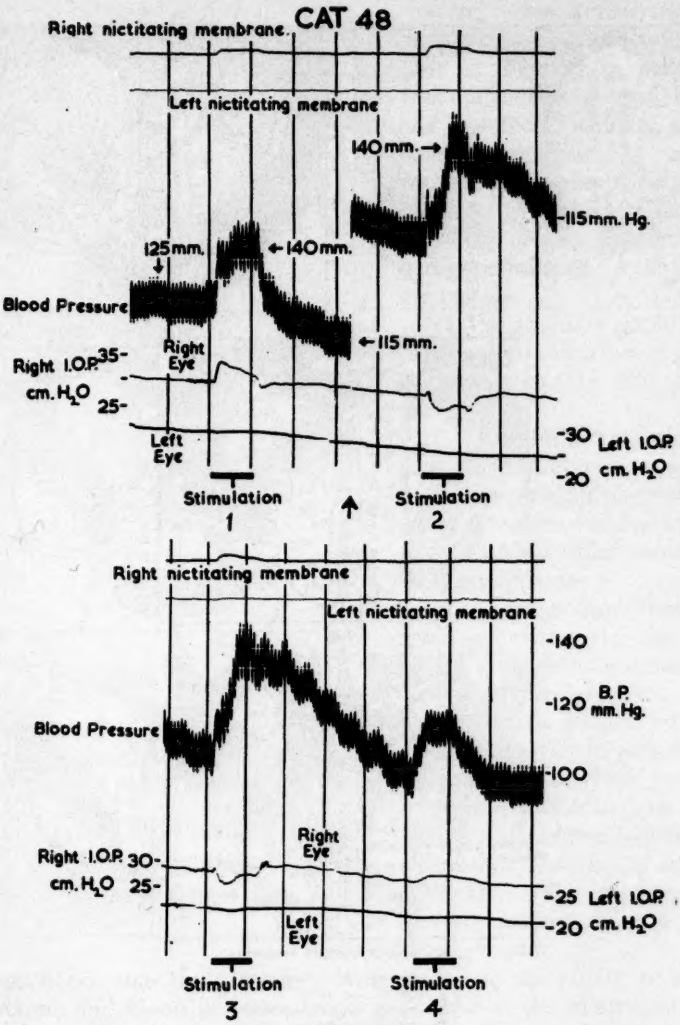


FIG. 11.—Tracings showing fall in intra-ocular pressure with a rise in blood pressure obtained from a limited area. The points stimulated are 1 mm. apart and only Stimulations 2 and 3 give the characteristic response. Interval between vertical lines represents 60 sec.

Localization: A11, R2 (see Fig. 12*c*)

Stimulation 1: H + 7½
Stimulation 2: H + 6½
Stimulation 3: H + 5
Stimulation 4: H + 4

(↑ = B.P. tracing adjusted)

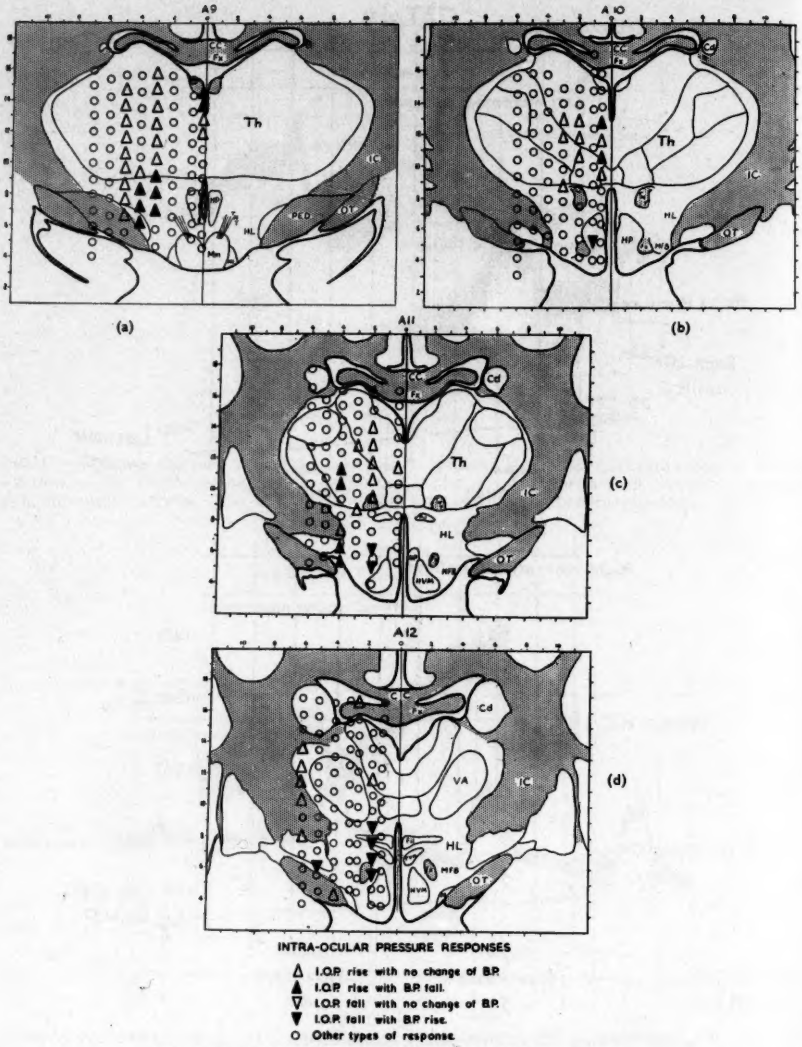
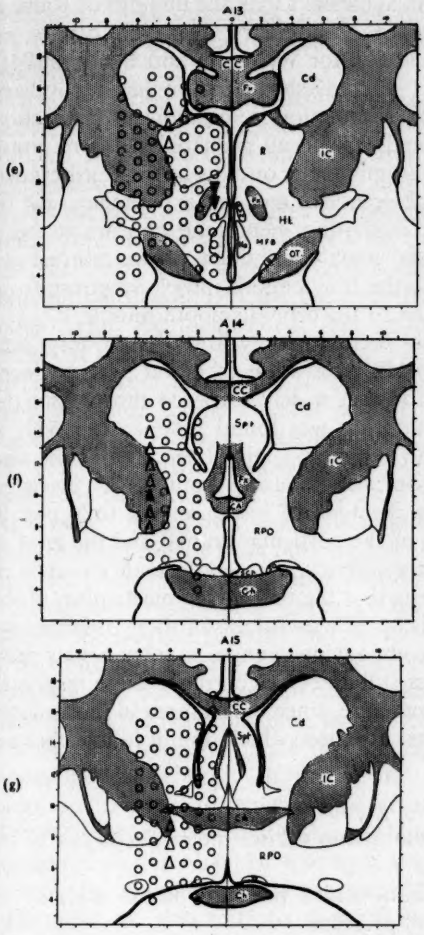


FIG. 12 (*a–g*).—Changes in intra-ocular pressure occurring independently of blood pressure changes in frontal planes A9 to A15. For explanation of lettered symbols see Appendix.

Discussion

The foregoing results have shown that electrical stimulation of the diencephalon causes changes in intra-ocular pressure, and many of these



changes reflect similar trends in the systemic blood pressure. This is broadly in agreement with the findings of von Sallmann and Lowenstein (1955), and we have encountered as wide a variety of type and pattern of response as did these authors. However, a strict comparison is hardly permissible for the following reasons:

(1) The stimulus employed by these authors differed in certain characteristics from that used by us;

(2) These authors examined the area in a different way, concentrating on a parasagittal plane 2 mm. from the mid-line as compared with our wider coverage of the diencephalon;

(3) These authors used the speed of change in the intra-ocular pressure as a criterion in classifying their responses, whereas our analysis is based primarily on the correlation of such changes with changes in blood pressure.

This has enabled us to recognize certain well-defined independent responses of which the most interesting is a fall in intra-ocular pressure accompanying a rise in blood pressure.

It was hoped that the subsidiary observations on the pupils, nictitating membranes, and blood pressure would be helpful in the interpretation of the responses of the intra-ocular pressure, and these observations will now be discussed. With regard to changes in the pupil, it was pointed out earlier that our method favoured the observation of pupillary dilatation, the pupils being usually small when the experiment had reached the stage at which the stimulations were commenced. Thus, whilst the slightest pupillary dilatation was readily seen, a corresponding degree of constriction would have passed unnoticed. In general, dilatation was elicited from points over a wide area, but the greatest responses were obtained from the posterior

half of the hypothalamus. This is in agreement with the findings of Ranson and Magoun (1933). The occurrence of pupillary dilatation cannot be taken as evidence of sympathetic activity, for Weinstein and Bender (1941) and Carlson, Darrow, and Gellorn (1940) have shown that in the cat pupillary dilatation resulting from diencephalic stimulation is not abolished by section of the cervical sympathetic trunk, and that, in all probability, the response is partly due to inhibition of the parasympathetic outflow in the third cranial nerve. We have confirmed these observations and our experiments will be reported later. Retraction of the nictitating membrane appears to be a more reliable indicator of sympathetic activity, although, as was pointed out earlier, it is necessary to distinguish the true smooth muscle response from that due to striated muscle connected to the orbital smooth muscle.

Whereas pupillary dilatations were elicited mainly from the posterior half of the hypothalamus, the points yielding elevation of blood pressure were not limited to this region but were in fact widely scattered throughout the diencephalon. No consistent relationship was found between the type of variation in the blood pressure and the region stimulated, both rises and falls sometimes being obtained from neighbouring points. A review of our results strongly suggested that the type of response was to a certain extent determined by the reactivity of the particular animal and the level of its blood pressure. This lack of consistency, as regards both the type of response and its localization, suggests that the underlying mechanism of the response of blood pressure is complex. The usefulness of these observations in explaining the mechanism of accompanying changes in intra-ocular pressure is therefore limited, but there is still a need to correlate these responses of intra-ocular pressure and blood pressure, since the changes in intra-ocular pressure which are of greatest interest are those which do not follow changes in blood pressure.

These latter responses fall into two groups:

(1) those in which the intra-ocular pressure rises independently of blood pressure;

(2) those in which a fall in intra-ocular pressure occurs without an accompanying fall in blood pressure.

The abrupt nature of the independent elevation in intra-ocular pressure suggests that this may have been due to contraction of striated or non-striated muscle within the orbit, although a vascular cause cannot as yet be excluded. The subsidiary observations on blood pressure, nictitating membrane, and pupillary changes do not provide any clue to the mechanism. With regard to the independent fall in intra-ocular pressure, it was thought that this might be due to a fall in capillary blood pressure within the eye as a result of vasoconstriction brought about by increased sympathetic activity. This view is supported by the subsidiary observations, the fall in intra-ocular pressure being accompanied by a rise in systemic blood pressure, pupillary

dilatation, and sometimes by contraction of the nictitating membrane. This response has been investigated further and the findings will be reported subsequently.

In considering the localization of points yielding changes in intra-ocular pressure, it has already been pointed out that the blood pressure responses showed no pattern of localization, and therefore the same is true for such intra-ocular pressure responses as may occur as reflections of changes in blood pressure. With regard to independent rises in intra-ocular pressure, these were elicited from a fairly wide area, but in the main were limited to the thalamus; several points giving this response were found within the internal capsule and in the posterior hypothalamus in plane A9. On the other hand, the independent falls in intra-ocular pressure were confined, with the exception of one point in A12, to the medial part of the hypothalamus, from plane A10 to plane A13, and most of these points were closely related to the anterior column of the fornix. von Sallmann and Lowenstein (1955) also obtained independent rises in intra-ocular pressure from a wide area, predominantly from the thalamus, and our findings regarding the localization of this type of response are therefore in general agreement. However, while these authors reported independent falls in intra-ocular pressure from both the hypothalamus and thalamus, we obtained this response from the hypothalamus only, and never from the thalamus.

In view of our present ignorance of the mechanism of the independent rises in intra-ocular pressure and the wide area from which they were elicited, it is difficult to assess their significance. Combined rises in intra-ocular pressure and blood pressure were obtained from stimulation of many points throughout the hypothalamus, as reported by von Sallmann and Lowenstein (1955), who suggested that these effects were manifestations of a mass sympathetic discharge. If this is the case, then the independent fall in intra-ocular pressure which we obtained from a more circumscribed area in the hypothalamus may possess additional significance; we have already suggested that it may be due to a reduction in capillary blood pressure within the eye, and, in the presence of a rise in systemic blood pressure, this could be due only to a local vasoconstriction resulting from local sympathetic activity outweighing the effects of the general sympathetic discharge. The present evidence does not allow the conclusion that the distribution of this "local" sympathetic activity is confined to the ocular tissues.

The responses in which the changes in intra-ocular pressure merely reflect changes in blood pressure must be considered as non-specific, similar responses being obtained, for example, after a painful stimulus or in acute anoxia. On the other hand, the responses of intra-ocular pressure which occur independently of blood pressure are more specific and provide the only indication that the diencephalon might have a special role in the maintenance of the intra-ocular pressure. It is not certain, however, that

the pathways involved in these responses originate in the diencephalon, since it is possible that the effects were obtained from stimulation of nerve tracts running through the diencephalon and emanating from other nervous centres. Nevertheless, our findings are compatible with the view that the diencephalon influences the intra-ocular pressure, but they do not allow the conclusion that any such influence is in the nature of a *controlling* mechanism. Such a mechanism demands the existence of an afferent pathway from the eye to the diencephalon in addition to the efferent pathways. These latter are, in fact, the only parts of the mechanism which can be demonstrated by stimulation in the central nervous system.

Turning from these purely physiological considerations, it is not possible at present to see how far these findings are applicable to the aetiology of glaucoma, but it should be borne in mind in this connexion that they may have significance irrespective of the existence of any diencephalic *control* of intra-ocular pressure, as, for example, in explaining the precipitation of an acute rise in ocular tension. It is also reasonable to take into account, not only the centrally induced changes in intra-ocular pressure, but also the possible alterations in the vascular supply to the eye, which may be the more important feature in some forms of glaucoma by giving rise to defects in the visual fields as a result of relative ischaemia of the neuro-retinal elements.

We would emphasize, however, that these remarks are speculative and that no firm clinical inferences can be drawn at present, but the experimental finding that stimulation in the diencephalon does influence intra-ocular pressure undoubtedly encourages further investigation.

Summary

(1) The diencephalon of anaesthetized cats has been stimulated electrically. The intra-ocular pressure, systemic blood pressure, and movements of the nictitating membranes were recorded. Pupillary responses were also observed. The position of the tip of the electrode was confirmed histologically and the points from which responses were obtained were plotted on maps of the diencephalon.

(2) Pupillary dilatations were elicited from a wide area of the diencephalon, the greatest effects being obtained from stimulation in the hypothalamus in frontal planes 9 to 13 mm. anterior to the inter-aural line (A9 to A13). Dilatations were usually of equal extent in the two eyes. Pupillary constrictions were rarely found.

(3) Responses of the nictitating membranes were infrequent and small in magnitude, the most common being a small retraction.

(4) Simple rises and falls with some complex responses of the blood pressure were obtained from a wide area, but the type of response differed considerably from animal to animal. The most marked rises in blood

pressure occurred with stimulations in the medial hypothalamus in frontal planes A12 and A13.

(5) The responses of intra-ocular pressure were analysed with reference to the accompanying changes in blood pressure. In almost half the total number of stimulations, both intra-ocular pressure and blood pressure remained unchanged. In many instances in which responses were obtained, the changes in intra-ocular pressure were accompanied by changes in blood pressure in the same direction.

(6) Independent rises in intra-ocular pressure were observed, the blood pressure either falling simultaneously or remaining unchanged. These responses were obtained from widely separated points, mainly in the postero-dorsal region of the diencephalon.

(7) Independent falls in intra-ocular pressure formed part of a characteristic response-pattern in which there was an accompanying rise in blood pressure, pupillary dilatation, and sometimes retraction of the nictitating membrane. This was obtained from a fairly circumscribed area in the medial hypothalamus. It is suggested that the fall in intra-ocular pressure in this type of response is due to a reduction in the ocular blood supply.

(8) These findings are discussed with regard to the ways in which the intra-ocular pressure may be influenced by central nervous mechanisms.

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APPENDIX

LIST OF LETTERED SYMBOLS

CA	Anterior commissure
CC	Corpus callosum
Cd	*Caudate nucleus*
Ch	Optic chiasma

Fil	Nucleus filiformis
Fx	Fornix
Ha	Anterior hypothalamic nucleus
HL	Lateral hypothalamic area
HP	Posterior hypothalamic nucleus
HVM	Ventromedial hypothalamic nucleus
IC	Internal capsule
MFB	Medial forebrain bundle
Ml	Lateral mamillary nucleus
Mm	Mamillary body
OT	Optic tract
PED	Cerebral peduncle
PVH	Paraventricular hypothalamic nucleus
R	Nucleus reticularis
RPO	Pre-optic area
SCh	Supra-chiasmatic nucleus
SO	Supra-optic nucleus
Spt	Area septalis
Th	Thalamus
TMT	Mamillo-thalamic tract
VA	Nucleus ventralis anterior of thalamus

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FUCHS'S EPITHELIAL DYSTROPHY OF THE CORNEA*

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BEGINNERS in any branch of medicine are often accused of being too ready to diagnose rare diseases among patients afflicted with the common things. Bearing in mind, as we always should, that common diseases are often manifested non-typically, we must look with initial suspicion at any evidence pointing to a rarity. We know, for instance, that appendicitis can simulate all manner of recondite abdominal lesions, and that pneumonia emerging in bizarre forms may bewilder all but the most astute clinicians; and of course we have comparable pitfalls in ophthalmology. Nevertheless, I will not apologize for speaking about a rare condition. On the contrary, I want to emphasize the importance of Fuchs's corneal dystrophy. This disease is often missed, often enters into differential diagnosis, and it has been repeatedly confused with glaucoma. Therefore statistical tables concerning the relative frequency of eye diseases necessarily fail to convey the full significance of Fuchs's dystrophy in everyday clinical practice.

The main features of this malady are now well established. It affects both eyes, although one may be implicated earlier than the other, as obtains in so many bilateral diseases. Most of the victims are elderly, and women outnumber men in nearly all the recorded series. First the endothelium is attacked, then the epithelium, and finally the corneal substance. Failing vision is the cardinal symptom, and the causation remains obscure. Before we proceed to more detailed description, it will be convenient to recall the pioneer work upon this subject.

BRIEF REVIEW OF THE LITERATURE

Fuchs's original account of epithelial dystrophy (Fuchs, 1910) is a *locus classicus* in ophthalmic literature. There we find most lucidly marshalled all the essential points except those endothelial changes which were not recognizable until slit-lamp microscopy had been evolved. Fuchs describes the loss of corneal sensation, the development of epithelial vesicles spreading from the centre to the periphery of the cornea, and the subsequent invasion of the substantia propria. His paper is based upon thirteen elderly patients, nine of them women, set forth in detail. Although Fuchs did not possess that apparatus which enables us to scrutinize the living corneal endothelium, he was able to foreshadow that an endothelial defect might be responsible for this strange clinical entity. In his Bowman lecture delivered eight years earlier (Fuchs, 1902), he had already made brief mention of a

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strange condition simulating glaucoma in the corneae of elderly patients; and he speculated concerning the possibility of an endothelial change as the primary lesion. Those remarks, if they are read in conjunction with his 1910 paper, clearly show that Fuchs was already on the track of his now famous dystrophy, but he did not follow up this brilliant guess about the endothelium. The only fragment of cornea which he could secure for histological investigation was a disc consisting only of the superficial layers. Even a whole-thickness corneal section would probably have failed to display the endothelial changes after exposure to the chemical processes of fixation.

Kraupa (1920) was the first to publish a description of the endothelial changes which are now known to precede those of the epithelium in Fuchs's so-called epithelial dystrophy. It will be recalled that Gullstrand (1911) demonstrated his slit lamp in Heidelberg at the International Congress, just a year after the publication of Fuchs's classical paper. During the ensuing years, in the face of shortages and distractions created by the 1914–18 war, various improvements were wrought in Gullstrand's lamp. Kraupa made good use of these devices, and reached the correct conclusion that the endothelium is the first layer to be implicated in this disease. At the same time Vogt was scrutinizing the endothelial changes in Fuchs's dystrophy, though his observations were not published until the year after Kraupa's paper had appeared. Vogt (1921) gave, as might be expected, a beautifully vivid description, likening the altered endothelium to powdered bronze dusted upon the back of the cornea.

Vogt's powdered bronze phenomenon is essentially due to disintegration of the cells composing the endothelial mosaic, which are displayed by slit-lamp microscopy of the posterior corneal surface in the zone of specular reflection. In a minority of cases, endothelial disintegration is not the first sign produced by Fuchs's dystrophy. Instead, we may find large apparent holes in the endothelium of the axial region. Similar but smaller "holes" have been proved to consist of localized backward bulges of Descemet's membrane into the anterior chamber. Naturally the endothelium at the back of each bulge is thrown out of focus in relation to the rest of the endothelial sheet, and so we get the illusion of "holes". The same structural explanation holds good for the larger, axial "holes" occasionally found in early Fuchs's dystrophy. In this context it is interesting to recall the contribution of Graves (1924). Graves had assembled some bilateral cases of these multiple endothelial warts in elderly people, some of whom displayed epithelial vesicles; and he came to realize, when his paper was nearly completed, that he was dealing not with a new entity but with instances of Fuchs's dystrophy. Within the next year or two Friedenwald and Friedenwald (1925), Gifford (1925), and Sallmann (1926) all produced work to confirm that the endothelium is the first layer to be involved. Further striking testimony was supplied by Paufique (1951), who noted that attempts to relieve the victims by a superficial lamellar graft were foiled by transudation of aqueous through the abnormally permeable endothelium; but the question of surgical treatment will be considered later.

Aetiology

In the last quarter of a century I have been able to see at least a hundred instances of Fuchs's dystrophy, some of whom have been other people's

patients sent for a second opinion. Of the 64 coming directly under my care, 49 (73 per cent.) have been women, and fifteen (27 per cent.) men. In Fuchs's original but shorter series, the relative percentages were similar, *viz.* 69 for women, 31 for men. I know of no substantial collection of cases in which the females do not greatly outnumber the males, and it is now generally agreed that Fuchs's dystrophy is commoner in women than in men, although this aspect of the aetiology has not so far thrown any light upon the causation.

The next aetiological point to be considered is the age at onset. Among the first five patients I saw, the average age was 69 years. Some of them showed a late stage of the disease, and must already have been affected for years. Since then I have several times discovered early Fuchs's dystrophy during routine examination of patients not producing any symptoms. Therefore some reduction must be made from the average age of observed victims if we want to estimate the true average age at onset. Even after due allowance was made for this consideration, I was led to conclude that the disease was rare before the age of 60 years, and I never saw a single instance in a patient less than 50 years old until 12 years ago, when to my astonishment I found the whole fully-delineated picture in both eyes of a 36-year-old woman. Since then I have been able to see Fuchs's dystrophy in a further six patients under 40 years old. The youngest was a 34-year-old man free from symptoms, and 2 years later he had still experienced no difficulty, although the physical signs were certainly more pronounced. I often wonder whether the second world war has shattered a lot of our long-established conceptions about aetiology. For example, most of us used to suppose that the older generation virtually monopolized basal-celled carcinoma of the eyelids, but since 1939 I have seen it in a number of patients less than 30 years old. We can still regard Fuchs's dystrophy mainly as a disease of old people, but it can no longer be ruled out as a possible explanation for visual failure in the lower age groups.

Having said that Fuchs's dystrophy is commoner in old than in young people, and that females are more susceptible than males, we arrive at the clouds of speculation if we continue to discuss aetiology. Treacher Collins (1907) described changes in the corneal epithelium associated with myxoedema and responding to the administration of thyroid extract, but this treatment fails to disperse Fuchs's dystrophy; and indeed these corneal lesions exhibit many points of difference from each other. Dystrophy of the corneal epithelium has also been found in cases of myotonia atrophica, but no particular systemic disease is typically linked with Fuchs's dystrophy; nor can Fuchs's corneal changes be dismissed as a manifestation of premature senility. Juler (1930) reported the disease in two sisters, but I know no other authentic example of familial incidence. No special climatic, occupational, or racial factors have been identified.

Symptoms

Fuchs's dystrophy, like most other bilateral diseases, may attack one eye sooner than the other, so that the earliest possible symptom is slight disturbance of vision in one eye. Sooner or later both eyes will become defective, but the march of disability may be exceedingly slow, and symptoms tend at first to be variable or even intermittent. Near objects look more blurred than distant ones, and many of the patients find that their sight improves as the day goes on.

When we recall the corresponding structural changes in the cornea we can perhaps account for this fluctuation. The endothelial changes, although they prepare the way for subsequent seepage of aqueous into the substance, do not of themselves obscure vision. Epithelial vesiculation, which becomes evident soon afterwards, is responsible for the blurring. Now it does not seem far-fetched to suppose that repeated blinks might temporarily clear the cornea by flattening the vesicles upon its epithelium. That supposition is borne out by clinical facts. Among several patients who had felt improvement in their sight as the day progressed, I was able to note that the signs as well as the symptoms were less obtrusive in the afternoon than in the morning. Evidently the eyelids as they move over the cornea with each blink produce an effect comparable with that of a light roller upon a piece of carefully clipped turf, so long as the vesicles remain small and delicate. As time goes on the epithelium coarsens, and changes develop in the corneal substance, so that vision remains bad all through the day.

Many of the patients suffering from Fuchs's dystrophy complain of seeing coloured rings around lights, a symptom which immediately raises the question of congestive glaucoma. It has been known for a long time that glaucomatous "haloes" are not the specific result of raised intra-ocular pressure. Epithelial vesicles, whatever may be their origin, can split white light into the colours of the Newtonian spectrum; and such vesicles can occur in a number of non-glaucomatous diseases, including Fuchs's dystrophy. Nevertheless the word "halo" continues to bias many ophthalmologists almost irrevocably towards a diagnosis of glaucoma. They see an elderly patient complaining of "haloes" and failing vision. Digital estimation of the intra-ocular pressure is notoriously uncertain. Even tonometry is far from precise. When once the mind has prematurely leapt to a diagnosis, rationalization can easily fill any gaps there may be in the evidence; and so it is not surprising that the literature contains numerous instances of people being wrongly subjected to drainage operations when they were in fact victims of Fuchs's dystrophy.

Physical Signs

Although the earliest signs of this disease are located in the endothelium, a large majority of the patients already show epithelial changes by the time

that a diagnosis can be made. Early endothelial changes in Fuchs's dystrophy do not disturb vision, and remain undetected unless the patient happens to come under slit-lamp scrutiny. Not uncommonly, however, we see the disease limited to the endothelium in a second and less affected eye, when the other and earlier affected eye shows epithelial signs as well.

The commonest endothelial change is disintegration of the cells, so that, when we focus on the posterior surface of the cornea in the zone of specular reflection, there is no golden mosaic. The normal tessellation is replaced by those amorphous red-pepper granules which Vogt likened to powdered bronze. One source of fallacy must, however, be borne in mind. Slit-lamp examination of elderly people nearly always reveals upon the hind surface of the cornea a few granules of iris pigment. Even in younger subjects we may discover similar particles aggregated into a Krukenberg's spindle; but this phenomenon should not be confused with endothelial dystrophy. Granules scattered by the iris pigment are never so abundant as to hide the whole of the endothelial sheet; and if we focus the posterior surface of the cornea in the zone of specular reflection away from the densest granular clumps, then we shall readily identify the mosaic pattern.

A minority of sufferers from Fuchs's dystrophy at first display large axial gaps in their endothelial tessellation. These apparent holes are, as we have already seen, due to localized backward bulges of Descemet's membrane together with the corresponding portion of endothelium. Although they do not directly impair the visual acuity, such interruptions in the endothelial mosaic are important in that they foreshadow more serious changes. Sooner or later the aforementioned endothelial disintegration will be evident, and by that time epithelial signs may have emerged.

Fine regular vesiculation in the axial region of the epithelium soon follows the endothelial changes in Fuchs's dystrophy. At this stage the patient may still be free from symptoms and in some instances the possibility of disease may be hinted by faint turbidity of the corneal axis examined with focal illumination and a uniocular loupe. The slit lamp will now clinch the diagnosis by displaying the characteristic endothelial lesions. It will be recalled that faint bedewing of the limbal epithelium is a physiological sign, but this entails no confusion with Fuchs's dystrophy, because the early epithelial changes in Fuchs's disease mainly implicate the axis, and fade away towards the periphery.

Alterations in the substantia propria are not long delayed when once the disease has invaded the endothelium and epithelium. Nearly all authorities agree that the main result of the endothelial disintegration is to render the hind layers of the cornea more permeable by the aqueous fluid. Swelling, striae, and irregular opacities, which typify Fuchs's dystrophy in the corneal substance, are attributable to aqueous percolating into and between the layers of the substantia propria.

Meanwhile, the anterior surface lesions are not stationary. The walls

of adjacent epithelial vesicles tend to undergo absorption, thus forming bullae of variable size. When the larger blebs give way, corneal ulcer may be simulated, and sometimes the tags of loosened epithelium abortively proliferate, as in keratoconjunctivitis sicca (Sjögren's disease). These patients run the risk of being subjected to carbolization and other heroic remedies; and here let us insist that the victims of Fuchs's dystrophy respond badly to physical and chemical trauma.

Loss of corneal sensitivity is often mentioned as an important sign of Fuchs's dystrophy, but I suggest that we should write off this item of evidence for two reasons. First, its validity is questionable by reason of the many other forms of degenerative and inflammatory corneal trouble in which the surface sensitivity is impaired. Secondly, the diseased epithelium can readily become infected if we keep on jabbing it with pieces of cotton-wool merely to see whether sensation is registered. Another important source of danger is the tonometer, especially if this instrument be repeatedly planted upon the loose, vulnerable epithelium of patients suffering from Fuchs's dystrophy.

Advanced cases of this disease show dense opacity of the substantia propria, so that the endothelial lesion will be masked. Sooner or later, in patients who live long enough, the anterior layers of the cornea will undergo hyaline degeneration followed by calcareous change. Flakes of calcium compounds may be shed off into the conjunctival sac, and the corneal surface is irregular. Corneal ulcer can occur as a complication, but not as often as might be expected, considering the insensitive and friable state of the epithelium in Fuchs's dystrophy. Peripheral new vessels are a late and by no means invariable manifestation of the disease.

Illustrative Case

The case which I will now describe had been previously missed by two colleagues, but I am well aware that I must have been guilty of similar lapses in the past. People who come in search of a further opinion often put us on our mettle, because we can all feel a slight feline thrill at finding something which eluded the other doctor. This patient was a healthy-minded, busy, highly-educated woman, 67 years old, who had become increasingly aware, for the last year, that it was difficult for her to read *The Times* newspaper in the morning, although she could manage quite well later in the day. The ophthalmologist whom she first consulted assured her that there was nothing organically wrong, and he went on to advise that she had been overworking and would soon be restored by a holiday. Having found the situation unchanged when she came back from her holiday, she went to see a second ophthalmologist, but he deeply offended her by suggesting that a psychiatrist was the proper person to deal with her problem. She assured me that she had never felt any inclination to be a hypochondriac, and she described her matutinal reading handicap lucidly, without any neurotic overemphasis.

With small correcting-lenses each eye read 6/6, and I found no abnormality in the fundi or media, but inspection of the corneae with the uniocular loupe and focal illuminator revealed faint but unmistakable turbidity of the axial surface. Then slit-lamp microscopy made the diagnosis certain. In both corneae the endothelium was amorphous, and fine regular vesicles covered the axial region of the epithelium. I told her that gentle eye massage through the closed lids for a few minutes every morning would probably be a help for some time to come; and in fact this simple palliative device did enable her to

resume her morning study of the newspaper. Incidentally her joy at being released from the stigma of anxiety neurosis and the threat of psychiatry saved her from the disquiet which she would otherwise have felt about the revelation of eye disease.

Differential Diagnosis

We have already seen that advanced Fuchs's dystrophy can be confused with corneal ulcer and with Sjögren's disease, and that its early signs may easily be missed in the hurry of everyday clinical practice, but of course the most important diagnostic relationship is with glaucoma. Nowadays many of the glaucoma suspects inhabiting large cities will undergo minute investigation at special clinics. Provocative tests and other checks by trained observers have presumably lessened the chance of drainage operations being mistakenly done for eyes that exhibit Fuchs's dystrophy; but we must still be particularly vigilant when we are confronted with people in the higher age groups who complain about haloes and failing vision. Oedema of the corneal epithelium linked with these symptoms does not necessarily mean that there is or has recently been a rise in the intra-ocular pressure. Those who study the literature concerning Fuchs's dystrophy will find solid grounds for believing that the disease can readily be confused with glaucoma.

Treatment

Innumerable kinds of topical and systemic therapy have been tried for this disease. Dionine, holocaine, yellow oxide of mercury, hot applications, and various subconjunctival injections have all had their advocates. Sclerectomy, sclerotomy, iridectomy, lid suture, and grafting of mucous membrane after partial removal of the conjunctiva, are among the many procedures that have been tried; and one surgeon went so far as to apply tincture of iodine to the corneal surface after scraping away the epithelium. Systemically glycero-phosphates have been given, and many kinds of organo-therapy, including cortisone in recent years. The number and variety of these remedies coupled with the fact that most of them have fallen into desuetude supply ample comment.

Until recently there were only two ways in which one might help the people suffering from Fuchs's dystrophy. First of all, having established the diagnosis, one could ensure that they were not subjected to drastic topical measures, including drainage operations, likely to make them worse. Secondly, one could give simple advice about palliative measures, especially massage through the closed lids, and the discretional use of normal saline and parolein drops. Bearing in mind that the onset of Fuchs's dystrophy is usually late, we have the right to assume that many of the victims will die before being seriously handicapped by these slowly progressing corneal changes. Therefore palliative treatment is still important, but in the last few years the prospect of benefit from surgery has brightened.

We have already referred to the disappointing results of corneal grafting, whether whole-thickness or lamellar, in cases of Fuchs's dystrophy, even when those operations were done by grafting experts with a high record of

success in other corneal conditions. Paufique (1953) became more and more convinced that permeability of the diseased endothelium was radically to blame in cases of Fuchs's dystrophy. Meanwhile he had achieved more success than at first he had dared to hope in certain cases of opacity involving the whole anterior corneal surface. He found that removal of the diseased layer was followed by total regeneration of the epithelium within a few days, and he conceived the hope that healthy endothelium might similarly re-form after removal of its diseased remnants. Animal experiments showed that Descemet's membrane and its endothelium could regenerate in just under 3 weeks. Paufique was well aware, however, that the membrane adheres firmly to the posterior layers of the substance. Therefore he was afraid that the upheaval entailed by scraping-off Descemet's membrane might preclude success. In fact it turned out that the attachment of Descemet's membrane is remarkably loosened in Fuchs's dystrophy. Therefore Paufique found it quite easy to scrape off the diseased posterior layers with a Meibomian curette passed through the temporal side of the limbus. Soon after this operation the substantia propria inevitably swells up, but that phase passes and the results have so far been encouraging. Paufique did not advocate this operation for slight, early instances of Fuchs's dystrophy, nor could we expect it to benefit those patients in whom all layers of the cornea display gross disease; but already there are good grounds for hope in properly selected cases of this hitherto hopeless condition.

General Conclusions

Fuchs's dystrophy is a rare disease in a small organ, but there is far more to be said about it than has been written above. I could have given descriptions of a dozen illustrative cases instead of a single one. I might have dwelt at length upon the morbid histology, or perhaps discussed in greater detail the theories of origin, but many of you will be able to fill in gaps from your own experience or from your acquaintance with the literature. At any rate I hope I have been able to convince you, those who were not already convinced, that Fuchs's dystrophy is an important disease; and it is assuredly a humbling thought for us all that, in spite of research by generations of ophthalmologists in many lands, the origin of this condition is still an enigma.

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Brit. J. Ophthal. (1957) **41**, 541.

A PEDIGREE OF ANOPHTHALMOS*

BY

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THE difficulties inherent in any assessment of the exact status of a case of anophthalmos is brought out by the following report of a family in which one child and two of its sibs were affected, but no ocular anomalies were found in the ascendants. The pedigree is shown in the Figure.

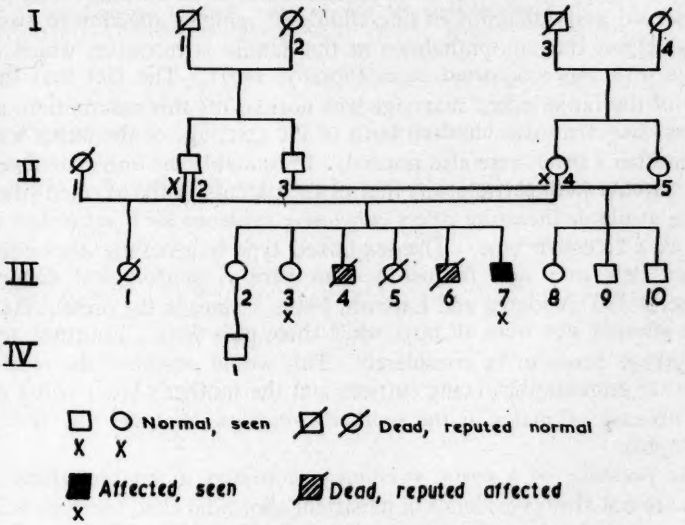

FIGURE.—Pedigree of a case of bilateral anophthalmos.

Case Report

A male infant aged 9 months (III, 7) was seen with a history of having been born blind. On examination he was found to have very small palpebral fissures with the eyelids very deeply set. The lower part of the lower lids and the upper part of the cheek showed a soft globular bluish swelling fairly well demarcated. On opening the lids there was no eye to be seen and the orbit appeared to be lined by the conjunctiva. The appearance was similar on both sides—the left side showing a more marked swelling. The child was otherwise normal. 6 months later he was brought back because the swelling

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on the left side had suddenly increased. An exploratory puncture of the cystic swelling showed old blood which was evacuated.

The mother gave a history that two other boys (III, 4 and 6) born to her had been similarly affected, but had both died in infancy. A third child, a girl (III, 5), who also died in infancy, had normal eyes. No history of a similar condition in the ascendants or collaterals could be established.

The father (II, 2), who was aged 50 years, had full vision in each eye. The eyes were normal in size, emmetropic, and free of any abnormalities.

The mother (II, 4), who was aged 33 years, also had entirely normal eyes, normal in size, emmetropic, and with full vision.

Discussion

In view of the family history, causative environmental factors can be excluded from further consideration. A search for ocular anomalies in other members of the family proved difficult; only one sib (III, 3) of the affected boy could be seen, and she was found to be normal. The findings —observed anophthalmos in one child and reputed affection in two more sibs—suggest that anophthalmos in this family is recessive, which is consistent with other reported cases (Sorsby, 1951). The fact that the only child of the father's first marriage was normal fits this assumption, as does the fact that the three children born of the marriage of the father's brother and mother's sister were also normal. Presumably the only marriage where both parents were carriers was that of the parents of the affected sibship.

The available literature offers conclusive evidence for a sex-linked type as well as a recessive type. The sex-linked type is generally associated with mental deficiency and frequently with various neurological disturbances (Roberts, 1937; Sjögren and Larsson, 1949). Since in the present family the three affected sibs were all boys while three girls were all normal, recessive sex-linkage needs to be considered. This would postulate the mother and maternal grandmother being carriers and the mother's sister being normal. The absence of males in the mother's sibships precludes any test of this assumption.

The presence of a cystic swelling is common in anophthalmos. Such cysts are not always evidence of persistent choroidal cleft, for cysts may form without any developmental anomaly of the choroidal cleft, as is shown by the experimental observations of Chase and Chase (1941) on recessive anophthalmos in the mouse. In this condition the primary optic vescicle is formed normally and development proceeds normally until about halfway through pregnancy. At this stage, instead of further differentiation, regressive changes set in, leaving a variable degree of cyst formation. A cystic swelling can be taken as evidence of failure of closure of the choroidal cleft if microphthalmos is also present, but a microphthalmos is not in itself evidence of persistent choroidal cleft, since it may well be an abortive anophthalmos (as is seen in strains of anophthalmic mice). The significance

of anophthalmos and microphthalmos becomes still more complex when it is realized that these anomalies may be part of wide-spread defects bordering on the disorders seen in such conditions as the Laurence-Biedl syndrome (François, 1953). Anophthalmos corresponding to the experimentally observed anophthalmos in the mouse appears to be determined in the human foetus by anomalies at the end of the first month of pregnancy (Moretti, 1955). In these cases, as in the experimentally observed mouse, there is no gross maldevelopment of the brain. Gross cerebral anomalies would seem to occur if there is anomalous development at an even earlier stage, so that a monster is born rather than a defective viable child.

I should like to thank Professor Sorsby for his help in the preparation of this paper.

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ACUTE OCULAR ONCHOCERCIASIS AND ITS TREATMENT*

BY

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THERE are some discrepancies and a little ambiguity in the various descriptions of the clinical signs and symptoms and the course of ocular onchocerciasis. In this paper it is intended, in the light of our experiences in West Africa, to describe those manifestations of the disease in the eye which we have seen in an acute phase, and which if untreated progress in most instances to blindness. This type of blinding lesion at its simplest is limited to the cornea and the iris; adjacent tissues may, of course, be primarily or secondarily involved. Wholly on clinical grounds, we categorize the lesions as a limbitis, a sclerosing keratitis (due to the formation of pannus onchocercosus), an anterior uveitis (iritis, iridocyclitis), and a posterior exudative uveitis.

Before describing these conditions in detail, it would be as well to mention some features normally present in the African eye which may confuse the issue. Pigmentation of the eye being dense, it is not surprising that any disorder such as chronic irritation will produce aggregations of pigment and a local increase in its density. We are thinking here of irritation due to the climate and to the presence of hot winds with a high dust particle. There seems little doubt that this leads to an increase in pigmentation of the interpalpebral conjunctiva, and it is also probably the cause of the extremely frequent occurrence of pingueculae. These pingueculae show histologically (as we discovered) a well-defined hyaline plaque lying in chronically infiltrated fibrous tissue, surrounded in some instances by squamous epithelium, and within which there are several groups of fragmented, degenerate, swollen, coiled, collagen fibres. This being the characteristic histological picture of a pinguecula, there is no need for us to hypothesize that invasion of the subconjunctival space by microfilariae plays any part in the pathogenesis. The same argument holds good for early pterygia, which are also not infrequently found, although invasion of the cornea by this benign tumour is not nearly so common as in the Middle or Far East. We did notice, and have observed elsewhere (Rodger, 1957a), that the association of pigmentation of the lower bulbar conjunctiva with folds in that membrane is a more frequent finding in vitamin-A deficient areas than in areas with a plentiful supply of this essential vitamin. An interesting condition, also mentioned before (Rodger, 1957a), and called arcus tropicalis, may have the same

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origin. In this condition, the arcus differs from arcus senilis in that there is no clear zone of cornea between the opacification and the limbus, and that its distribution is entirely superficial. The limbal pigment fuses with it.

There are one or two other pigmentary differences between the eye of an African and that of a European. Chromatophores are present in greater quantity around the perforating arteries, giving rise to an interrupted arc of dense pigment spots on the upper bulb (Fig. 1). The entire limbus is usually heavily pigmented with frond-like aggregations around the capillaries, and with the slit lamp an invasion of the cornea by pigment granules may be seen. It was noticeable that corneal neovascularization from the limbus is absent in the African eye, despite the fact that the average intake of riboflavin is only about 75 per cent. of the international requirement. Spots of pigment granules were also seen on numerous occasions passing for several millimetres over the surface of the cornea. Whether or not this migration of pigment cells is due to minor abrasion of the epithelium, we cannot say, but it seems to have no particular significance. In a very few cases, a sparse but uniform distribution of pigment granules over the entire surface of the cornea was seen in eyes that were apparently quite healthy. In the anterior uvea we observed several times an atavistic pupillary fringe, especially at the upper arc, which might be confused with old inflammatory efflorescences. In the iris stroma, it is almost the rule in the African eye for there to be a deficiency of pigment at the bottom of the crypts, and at the foot of many of the furrows. These anomalies have been selected, because here and there in the literature they have been attributed to onchocerciasis. There is no doubt that, at times—for example, when areas of depigmentation are seen

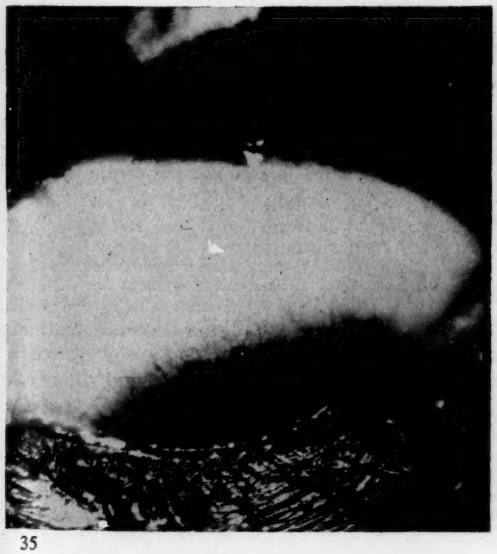

FIG. 1.—Normal Negroid pigmentation at the limbus spreads sometimes as much as 10 mm. from the cornea, as here, fading off into the white sclera. The pigment around the perforating anterior ciliary arteries is dense and circumscribed as shown.

in the iris stroma in association with other obvious signs of an onchocercal anterior uveitis—it is difficult to reach a decision.

I. Onchocercal Limbitis

This condition is seldom severe; it is characterized by discomfort more often than by pain, but it can be acute, and usually is so when a keratitis supervenes. It is due to the presence of microfilariae in the subconjunctival space, and to the death of some of them at the limbal cul-de-sac. Sometimes the patient complained of formication of the conjunctiva, but as this information was only able to be elicited by direct questioning, there must be some doubt about it. The patient suffers from lacrimation and photophobia. The clinical appearance is often very like that of a virus keratoconjunctivitis, inasmuch as there is dusky hyperaemia of the bulbar conjunctiva, a watery secretion, discomfort, and little else. However, examination with the slit lamp shows a degree of chemosis at the limbus, and in the adjacent region of the cornea a characteristic opacification which consists of a number of discrete grey dots (Fig. 2). We have described this in our notes as a "snowstorm" zone, a term which will be of use later; a few loops sprouted from the limbal vessels may be seen lying within this opacification; they pass above Bowman's membrane. We have never observed a limbitis of this type in the upper half of the cornea; it always occurs in the lower half, and may or may not involve a considerable portion of it. The commonest site of all is in the region of an inner or outer canthal pinguecula or early pterygium. The limbitis may advance to a definite sclerosing keratitis, or it may become quiescent. In the latter event it can either resolve completely, or leave behind some diagnostic evidence in the shape of a small residual sector of faint corneal opacification, frequently pigmented.

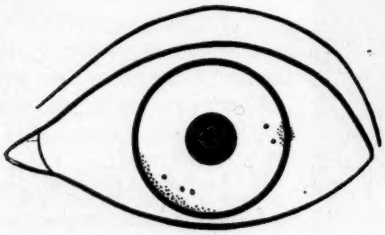

FIG. 2.—Onchocercal limbitis with an early tongue of pannus onchocercosus at 3 o'clock. The limbus at 7 o'clock is red and chemotic; in the cornea at this site there is a crescent of grey opacification (the snowstorm effect), and there are also a few punctate corneal opacities.

II. Onchocercal Sclerosing Keratitis

With the appearance of pannus onchocercosus, the condition becomes acute for a while at least. The keratitis frequently commences at 3 or 9 o'clock where tongues of the pannus onchocercosus invade the cornea (Figs 3 and 4); in the end they may meet at the centre (Fig. 5). Another common appearance of the sclerosing keratitis is as an apron of pannus around the lower half of the cornea (Fig. 6); this lesion also advances towards the pupillary area. Several tongues of pannus can appear at the same time in the lower half of the cornea, all of them maybe becoming confluent in the end.

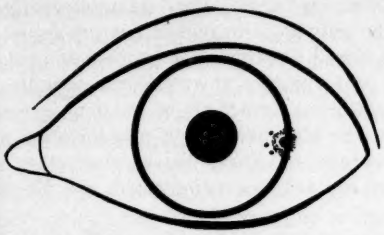

FIG. 3.—Early stage of onchocercal sclerosing keratitis, originating at a pinguecula. Three zones can be seen: an advancing "snowstorm" edge, a dense white middle zone, and a pigmented basal zone. A few punctate opacities are related closely to the advancing edge.

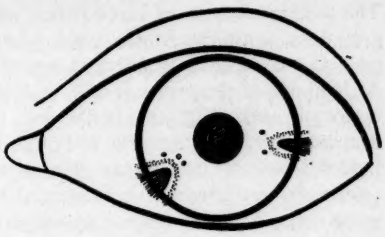

FIG. 4.—Two tongues of pannus onchocercosus.

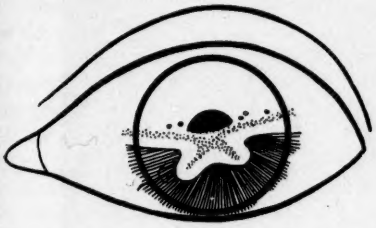

FIG. 5.—An advanced case of onchocercal sclerosing keratitis formed by the fusion of three separate tongues of pannus. The characteristic zones comprising each tongue are shown here, but the picture is often less clear-cut.

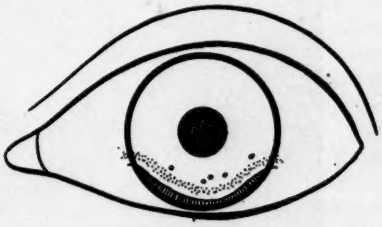

FIG. 6.—An apron of pannus onchocercosus, which has developed from a limbitis. Although punctate opacities related to pannus have been drawn in each instance, they are not always present.

When the condition is allowed to advance unchecked, the end-result is total involvement of the cornea; on many occasions we have seen such a pannus advance until all that was left was a clear area at 12 o'clock (Fig. 7); this is quite a common finding.

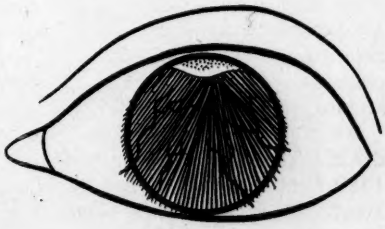

FIG. 7.—The end-result of onchocerciasis of the cornea. Large vessels have appeared superficially in the pigmented basal zone. A view of the iris can often be obtained through the comparatively clear zone at 12 o'clock.

The external appearance of the pannus onchocercosus is fairly characteristic: it lies at first between the epithelium and Bowman's membrane, as would a pannus degenerativus, but differs from the latter in being vascularized. Subsequently, it may break through Bowman's membrane or appear well below it. It is often associated (because the cornea is invaded in force) with interstitial areas of fibrosis.

The pannus consists of three zones: an advancing "snowstorm" zone of separate grey dots, a middle, white, zone, where the individual opacifications are densely packed, and a basal pigmented zone, which well illustrates the propensity in the African eye of the pigment cells to follow in the path of any traumatic or inflammatory process (Fig. 8). In the end, the epithelial surface above the pannus may become entirely pigmented, although it can be seen under high magnification to fade off towards the upper pole of the cornea. Corneal neovascularization is essentially restricted to the pannus, although in late cases, as indicated, new blood-vessels may break through into the stroma.

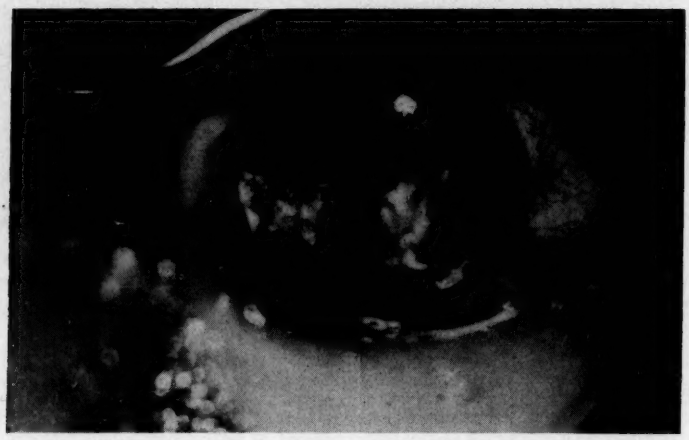

FIG. 8.—Advanced stage in the sclerosing keratitis of onchocerciasis. The three basic zones of pannus onchocercosus may be made out. There are some punctate opacities associated with the advancing edge of the pannus.

At all stages in this condition, one finds evidence of corneal degenerations. The keratitis is quite frequently associated with an anterior uveitis, and it appears from our records that degenerations of the corneal epithelium occur more frequently when such an association exists. Epithelial cysts and calcification may be seen; a band-shaped opacity is a fairly frequent finding in an early onchocercal sclerosing keratitis, even when the anterior uvea is not affected. Xerosis corneae is another common complication. One assumes that the major factor in all this is interference with corneal diffusion as a result of involvement of the limbal circulation.

An onchocercal punctate keratitis has been described as a separate entity, quite distinct from the sclerosing keratitis described here. In another paper (Rodger, 1957b), this lesion has been fully discussed in relation to the other types of punctate keratitis in Africa. There is no doubt that, in association with a limbitis or with tongues of pannus onchocercosus, punctate-like opacities are often seen. We should like to stress, however, before leaving this question, that a punctate keratitis in a quiet eye without concomitant signs of onchocercal keratitis or limbitis does not in our view occur. The diagnosis of an onchocercal keratitis does not, in short, depend upon punctate corneal opacities, an opinion also held by Hissette (1932).

III. Onchocercal Anterior Uveitis

As already mentioned, this condition can occur either by itself or in association with a sclerosing keratitis. It can be an extremely acute lesion subject to recrudescences. On the other hand, it often appears to remain sub-acute or chronic. We should like to describe—for it does not seem to have been described before—the acute manifestation.

The symptoms are those of an acute granulomatous iridocyclitis due to any cause. The iris is invaded, as we have proved to our own satisfaction by performing biopsies on several such cases, by living microfilariae, on the death of which gross exudation occurs at the pupillary margin. This is an important and specific sign of the condition. The exudation very quickly completely fills over the entire pupil. At the same time, the aqueous changes in nature and flare can be seen. Keratic precipitates are not a feature of the condition, but a few are sometimes seen in the centre rather than in the lower half of the cornea. The exudation over the pupil can increase in size until it either becomes fixed to the posterior surface of the cornea or spills over into the angle of the eye at 6 o'clock. As a result of this attachment, the pupil is characteristically deformed in that direction. Not surprisingly, as the greatest site of the inflammation is at the pupillary margin, the posterior pigmented fringe may become attached to the anterior lens capsule. In this, the characteristic lesion, the condition is strictly an iritis; however, very often the inflammatory process involves the ciliary body as well. As the entire picture occurs as a result of the disintegration of dead microfilarial bodies, it is invariably self-limiting. Recurrences, however, are common. After a period of a few days, even if untreated, the lesion usually begins to quieten down, adopting a subacute or chronic course. Unfortunately, the exudate often does not resolve to any extent at all; in short a very common end-picture is that of total occlusion of the pupil (Fig. 9). In several cases observed, where resolution did occur, it

FIG. 9.—End-result of onchocercal anterior uveitis. The pupil is occluded by a fibrous membrane, and is deformed by two anterior synechiae, the lower of which can be seen attached to the cornea at 3 o'clock in the neighbourhood of a tongue of pannus onchocercosus. Pigment invasion of the cornea below is the site of an old limbitis. The middle and basal zones of the pannus can be made out.

appeared to take place in a characteristic way; as a result of shrinkage, the pupillary membrane splits and patent sectors appear, usually at the pupillary margin. If the acute phase does not last long, then the lens behind is unlikely to be affected, and the patient will retain some measure of vision through these apertures in the inflammatory membrane. We have seen many cases where the entire exudative membrane disappeared, leaving in its wake a "rolled" border of organized exudate completely surrounding the pupil; in other cases not even this remained, the only evidence being the total depigmentation of the posterior pigmented fringe. The partial absorption and shrinkage of the anterior chamber mass (when it exists), which, as we have shown, usually remains attached to the pupillary margin, results in further distortion of the pupil in a downward direction. A not infrequent finding was that of a piece of organized exudate somewhere at the root of the iris whence it had fallen during the course of the acute phase forming an anterior synechia. Residual posterior synechiae with associated patches of iris atrophy were quite common, as was smearing of the entire pigment fringe over the anterior lens capsule. Pigment particles, fairly large in size, detached from the posterior pigment fringe, were quite often seen adherent to the remnants of the exudative membrane, or even to the synechiae. In many cases, the iris furrows become obliterated with pigment, the final appearance being that of brown velvet. The posterior attachments are sometimes associated with spots of opacification in the lens, which are sub-capsular. The characteristic miscellany of colours displayed in a posterior complicated cataract were also sometimes seen in association with precipitates on the posterior lens capsule, thereby furnishing further evidence that during the acute attack the ciliary body may be involved. The commonest type of complicated cataract was one where the anterior capsule had become white and thick, with exudative remnants attached, being separated from the shrunken lens body by white sterile fluid. It is tragic to think that often in such an eye the only residual defect preventing the subject from seeing is an inoperable complicated cataract. When the lens and ciliary body are involved, contracture of the cyclitic membrane leads to degeneration of the suspensory ligament, the lens frequently becoming subluxated or completely dislocated.

We never saw ectasias in association with onchocercal uveitis; nevertheless it is true to say that acute inflammation of the sclera is commonly associated with the sclerosing keratitis, the anterior uveitis, and the posterior uveitis now to be described. As a result of broad anterior synechiae at the periphery, secondary glaucoma is common.

IV. Onchocercal Posterior Exudative Uveitis

The descriptions of the posterior segmental lesion of onchocerciasis are so varied as to underline the fact that this lesion is the least understood. Through the many different descriptions one alone appears to be specific, and that is essentially a choroidal sclerosis involving the periphery either before or at the same time as it destroys the macula. This lesion is slow in onset and is never acute. It will be discussed in another paper. One reference only to this interesting condition will be made, and that is that the older view as to its aetiology is now out of favour; many more cases of the posterior segmental lesion have been found in association with low degrees of infection than with high, and in pathological specimens more eyeballs exhibiting this lesion have been found without microfilariae in the choroid

than with them. If the typical posterior segmental lesion of onchocerciasis does not necessarily depend, then, upon the presence of microfilariae in the tissues involved, what type of lesion does arise as a result of their death in the posterior uvea? We believe this is what happens:

In seven of 27 cases of acute anterior uveitis there was a concomitant posterior exudative uveitis. In four of these cases we were fortunate enough to enucleate the eyes. We were, therefore, able to confirm the presence of microfilariae in the posterior segment. Owing to the anterior involvement it was not easy, except in a few cases, to observe the fundus, and so the clinical description of this condition which we shall give now may not be as accurate as it should be. The retinal pigment epithelium reacted to the presence of the parasites (or their dead bodies) by the double process of degeneration and proliferation; this occurred more grossly than in the degenerative type of the posterior lesion. Large focal masses of pigment were scattered here and there, and occasional glimpses of the choroidal vascular system were observed; these vessels were usually healthy if somewhat engorged. In a few cases, small retinal haemorrhages were seen at the posterior polar region. Here and there, white patches indicated areas of choroido-retinal fusion, usually with retinal pigment heaped up at the edge. Exudates in the anterior chamber or even in the vitreous made it impossible to observe fuller details, but in one case the optic disc was atrophic and deeply cupped. Colloid bodies appeared to be common. They are, of course, not part of the acute picture, but were present in most of the quiescent cases of this condition that we saw. They may be taken as evidence of the previously acute inflammatory state of the uvea.

We have described briefly the appearance of the posterior uvea when that tissue is invaded by microfilariae. It is essentially part of an exogenous endophthalmitis. Recurrences must be common, and there can be no doubt this is a prolific cause of blindness. Quiescent cases with characteristic anterior lesions were extremely numerous, and at such a time the picture is that of a chronic non-specific uveoretinitis. The association with a typical anterior lesion, however, usually points to the diagnosis. In the absence of the latter, it is not possible to diagnose a non-specific posterior uveitis as due to onchocerciasis with certainty; nevertheless, it could happen.

Treatment of Acute Conditions

It is generally accepted to-day that the pathogenesis of onchocerciasis of the cornea and iris depends upon the death in these tissues of the parasites. There seems no reason to doubt this belief. At the outset of treatment, therefore, one is faced with this problem: if a drug is administered which kills the microfilariae, might this not exacerbate the symptoms and further increase the visual defect by increasing the number of dead microfilariae in the ocular tissues? A few such cases have been reported in the literature. For this reason we approached the problem very carefully.

To begin with, using diethylcarbamazine, we treated our cases of acute onchocercal kerato-uveitis with a standard course of 200 tablets, that is 10 g. Despite our fear that the ocular condition would worsen as a result of this treatment, there was no doubt that after 6 or 7 days it settled; on the other hand, there was little evidence of recovery of sight. In short, all that was achieved was a quiet, painless, blind eye. With the slit lamp we observed

that there was some degree of resolution of the keratitis, especially in the case of any punctate opacities lying close to the pannus, although little recovery at the pupil occurred.

Dissatisfied with our results, we turned to non-specific protein therapy, and here from the very first the effect was striking. We administered TAB vaccine intravenously, and also tried autohaemotherapy. The former was the more successful especially when we gave large doses. We started with 5 million units; a second dose of 10 million units was given, and finally one of 15 million units. As the effect of this therapy was immediate after the first injection, it was soon found best to standardize the treatment by administering a single dose of 10 million units of TAB vaccine, and following it up, as soon as the temperature had come down to normal, with the filaricide (10 g. Hetrazan). The effect of the protein therapy was to quieten the eye in a dramatic way. This was particularly true of the uveitis. The eye became quiet, and lacrimation and photophobia disappeared. A great deal of the ciliary and conjunctival hyperaemia vanished, and the cornea regained much of its lustre. When the filaricidal course was started, there was a reappearance of the acute symptoms, but it did not appear to be so distressing as when this drug was given without the initial protein therapy. Of course, control of this last finding is quite impossible, and the claim may not in fact be true. However, the ultimate result when protein therapy preceded filaricidal therapy appeared to be much better. Resolution of the occluding membrane was expedited, and return to a quiet eye occurred

TAB

EFFECT OF TREATMENT IN FI ES OF A

Serial No.	Age (yrs)	I.D.F.*	Lesion	Protein Therapy	Resu
15	35	31	Acute kerato-uveitis	10 ml. own blood intramuscularly	et eye
221	46	31	Acute kerato-uveitis	Nil	—
595	35	31	Acute anterior uveitis	20 ml. own blood intramuscularly 10 million units T.A.B. intravenous then given	dy quiet et eye
606	20	31	Acute keratitis	5 million units, no effect; 10 millio disappointing; 15 million unit T.A.B. intravenously	et eye
865	23	31	Acute kerato-uveitis	2·5 per cent. Cortone topically hr through the day; 25 mg. Hydr cortone daily for 7 days 10 million units T.A.B. intravenous	effect et eye

* Individual Density Fi er and Bro

sooner. The chance of preventing permanent total blindness was increased. Where cases have been reported in the literature of a slight improvement in the visual acuity after the excision of nodules, the modus operandi may well be that of a non-specific protein therapy resulting from the trauma of the surgical procedures.

The results of five of the more interesting cases in the clinical trials with this combined therapy are given in the Table.

Antihistamine and cortisone proved of little if any value. The depressing effect of the former is in itself a contraindication. We soon abandoned it altogether. Atropine we prefer to use after the TAB has quietened the eye, as many of the acute cases show a rise in tension.

Discussion

The lesions we have described are acute, and as such are not often seen. There is no doubt that in an out-patient clinic in a hospital in Africa they are extremely rare. In the course of our survey in Ghana (which was the most heavily infected region we visited) we noted 59 acute cases (excluding cases of limbitis). The disagreement in the literature whether or not ocular onchocerciasis ever has a really acute phase in the full meaning of the word will bear some reference now.

Hissette (1932) stated that, in many of his cases, although conjunctival hyperaemia and a ciliary flush were present, the iritis was very mild indeed. He said this was the characteristic picture, calling it a "torpid" iritis.

TAB

T IN FIVES OF ACUTE ONCHOCERCIASIS

y	Result	Effect of Hetrazan	Visual Acuity	
			Before	After
uscularly	et eye	Photophobia and lacrimation for 5 days	C.F.	6/60
	—	Gross oedema of lids and cheek Photophobia Blepharospasm Lacrimation for 7 days	H.M.	C.F.
uscularly travenous	ly quiet now	Acute flare-up after one tablet; course interrupted		
	et eye	Nil	C.F.	6/36
10 millio lion uni	et eye	Slight lacrimation only	C.F.	6/36
ically h ng. Hydr	effect			
travenous	et eye	Lacrimation and photophobia for 2 days	R6/12 L6/18	6/12 6/9

Density Fi er and Brown, 1956)

Strong, Sandground, Bequaert, and Ochoa (1934), who studied this condition in Guatemala in 1930, and later visited Hissette in the Congo, state that in Central America the ocular disturbances generally have an insidious onset. The only exception to this is the fact that photophobia was complained of in some of his cases. This picture is not one of a really acute condition.

Ridley (1945) is of the opinion that a chronic conjunctivitis with some acute exacerbations is the first ocular complaint, to which is added a degree of photophobia when corneal complications begin. Lesions of the anterior segment of the eye, he says, are usually insidious, giving rise to a slow but steady deterioration. In general, the finding of the more advanced ocular lesions in those of middle age shows, Ridley argues, that chronicity is the rule, and it is probable that the disease may run some 10 years before producing complete blindness.

Scott (1945) gives no indication of the clinical symptoms of onchocercal keratitis. He describes the iridocyclitis as developing with an accompanying photophobia, lacrimation, and ciliary flush, but holds to the published view.

Toulant and Boithias (1952), discussing the functional troubles which keratitis provokes, say they would be "less marked or less easily appreciated in the eyes of Negroes than they would be in the eyes of Europeans". This remark is not without some significance. They also note that, although they have seen the insidious iritis described by Hissette and the rest, they have also seen a plastic iritis with synechiae which must at one time have been acute.

This rapid survey of the literature shows the general consensus of opinion to be that the keratitis of onchocerciasis is a sub-acute condition, and that the anterior uveitis is an insidious one. A posterior uveitis of the type described here has not been described before. It is probably this condition which has led to such confusion in the many and varied descriptions of the posterior degenerative lesion of onchocerciasis, which has almost certainly quite a different aetiology.

The present paper shows clearly that acute ocular onchocerciasis affecting the cornea and the uvea are found in West Africa. There may be several reasons why this has not been noted before except in the conjectured reference to it by Toulant and Boithias. It is not to be forgotten, when dealing with the whole subject of onchocerciasis, that much depends upon the density of the infection of the subjects in the endemic areas, for the degree of invasion of the ocular tissues must surely reflect the density of the infection in the individual. We have shown to our own satisfaction that the pathogenesis of these ocular lesions depends upon the death of the parasites in the tissue concerned; this is the general view, and it should be readily accepted that where one microfilaria dies there will be a much milder reaction than where a dozen die, other things being equal. This is one possible explanation of the discrepancy in the various reports of the ocular symptoms of the disease.

We have visited areas of varying degrees of endemicity, and there appears to be some support for just such a point of view in what we found. In areas of low endemicity, the density of infection in the individual tended to be equally low and acute cases were few and far between. We have used an index to measure this density (Rodger and Brown, 1957). It was only when the Individual Density Figure (IDF) was 31 (the optimum figure), or very nearly so, that an acute eye was found. Nevertheless, the reverse is not true; many of the cases which clinically were chronic in type had equally high Individual Density Figures. In these latter cases, some other explanation must be found for the absence of acute symptoms. We believe that the answer is an immunological mechanism. This will be the subject of a further communication.

Although we have said that the intensity of the clinical symptoms depends upon either a quantitative or an immunological factor, there still must remain in territories where everybody over 20 has the disease, and where the Individual Density Figures are extremely high, many more cases of acute ocular onchocerciasis than those we find reported. The answer here, we feel, lies in the fact that the acute condition lasts for such a short time. During this period the subject has little inclination to attend a hospital. This is partly due to the inaccessibility of the villages and partly to the psychology of the people. When in pain, they hide. It is the acute case, as we have said, which is the more certain to progress to total blindness; we believe that sub-acute or chronic cases seldom do so, until an acute exacerbation occurs. Unless it is recognized that these different clinical manifestations of the disease exist, it would be quite easy to make the mistake of supposing that the course of the disease was always insidious before total blindness ensued. Although Ridley (1945) has argued that the finding of the more advanced ocular lesions in those over middle age proves that chronicity is the rule, it could be equally well argued that this finding is merely indirect evidence that acute blinding crises occur in all age groups. We believe that to be so. It greatly alters the prognosis and treatment.

As far as the clinical signs are concerned, there is on the whole fair agreement. We find it useful to distinguish between limbitis and sclerosing keratitis, because the former is not always an early stage of the latter; the condition in many cases never advances beyond the stage of a limbitis. Whether or not other workers agree with our view that a punctate keratitis is not in itself a manifestation of ocular onchocerciasis does not matter, because the condition is never a blinding one and so does not come into the scope of this paper. The proportion of blindness due to the keratitis and to the uveitis is almost equal, although taking those cases where both conditions exist, it is invariably true that it is the uveitis which leads to blindness. In a heavily endemic area in Northern Ghana, we noted 59 *acute* cases (excluding limbitis cases) of ocular onchocerciasis out of 450 sufferers from the disease. These 450 patients all had some defect of vision, in other

words they were a selected sample, although the causes of blindness were not restricted to onchocerciasis. Of the 59 acute cases, 27 suffered from onchocercal anterior uveitis (seven in association with posterior inflammation), 22 from the sclerosing keratitis, and ten from a mixture of both; 42 of the 59 were blind.

It is interesting to note the distribution of age:

In patients aged 15 years and under, there were six acute eyes: three of these were blind, the cause being a uveitis in one and a keratitis in two. All the three who retained some measure of vision suffered from the keratitis.

In the age group 16–25, there were fifteen acute lesions, of which seven were blind. The cause was a uveitis in three, keratitis in one, and kerato-uveitis in three. In the eight who retained their sight, the cause was a uveitis in two, a keratitis in five, and a kerato-uveitis in one.

In the age group 26–45, there were 33 acute lesions, of which 27 were already blind. The cause was a uveitis in fifteen cases, a keratitis in seven, and a kerato-uveitis in five. The seven cases exhibiting a posterior uveitis were all in this group. Of the six with some degree of visual acuity left, the cause was a uveitis in two, a keratitis in three, and a kerato-uveitis in one.

Finally, in the age group over 45, there were five acute cases of onchocerciasis, all of which were blind, four as a result of uveitis and one as a result of keratitis.

It is not intended, in giving the details in these groups, to make any strictly significant statistical deductions: nevertheless, it is obvious that acute lesions of ocular onchocerciasis are not uncommon in a heavily endemic area, and that they occur in all age groups. The average Individual Density Figure for those blinded by an anterior uveitis was 28, as compared with 26 in the case of those blinded by the keratitis; there is little material difference here. In those acute cases where some degree of vision was retained, the average Individual Density Figure was 22; neither is this, in our view, significant. What is significant is that the Individual Density Figures in all these acute cases were high. In fact, where it is low one would tend to be doubtful of the diagnosis. While the sclerosing keratitis is a fairly easy picture to diagnose even at an advanced stage, many of the cases of uveitis are not. This is particularly true in patients about 50 years of age where the disease in the skin may have died out. If there is any doubt in diagnosing uveitis in an eye now quiet, allowance being made for age, we personally should not feel like accepting that diagnosis unless there were nodules present, or at least one of the eight skin-biopsy series recommended by us (Rodger and Brown, 1957) was positive; the majority of quiescent uveitis cases seen are above 45 years of age, so this is quite a problem. The proportion of cases involving one eye to those involving two is in the ratio of 1 : 7. This factor should also be of some help in formulating a diagnosis based on the clinical signs.

Summary

(1) Acute manifestations of ocular onchocerciasis are seen as a limbitis, a sclerosing keratitis, and as an anterior and posterior uveitis.

(2) Differences in the African eye from the European eye that might confuse the clinical picture are discussed.

(3) The clinical signs and symptoms of onchocercal limbitis, sclerosing keratitis, and anterior and posterior uveitis are fully described.

(4) The lesions are usually seen in a sub-acute or chronic stage, but it is believed that in most of them there has been or will be an acute crisis at some time or other.

(5) After a few days the acute phase usually settles down, adopting once again its sub-acute or chronic course; in some instances, it is the acute manifestation which occurs first.

(6) It is during the acute attack that blindness is most likely to occur and consequently it is believed that it is most important to treat the acute cases.

(7) The treatment found to be most successful during the acute phase was an initial intravenous injection of 10 million units of TAB vaccine, followed as soon as the temperature was normal by 10 g. diethylcarbamazine (Hetrazan) orally. The eye becomes quiet within 12 hours of the non-specific protein therapy; although, on exposure to the filaricide, lacrimation and photophobia return, nevertheless the symptoms are not so acute as before. Resolution appears to be more likely to occur when protein therapy is administered first.

(8) A discussion of the clinical signs and symptoms in the light of the findings of other workers is given. It is noted that the general consensus of opinion is that the keratitis is a sub-acute condition and the anterior uveitis an insidious condition. The observations and results in the present paper show this not to be the case. Reasons for the discrepancies between the findings of various authors are put forward.

(9) It is suggested that the intensity of the clinical symptoms depends upon quantitative and immunological factors. The evidence of this is to be reported in a further communication.

(10) The description given of an exogenous posterior exudative uveitis due to onchocerciasis is believed to be the first publication of this finding.

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A NEW MEDIUM FOR THE STORAGE OF DONOR EYES FOR CORNEAL GRAFTS*

BY

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THE EXPANSION of modern keratoplasty has increased the demand for suitable donor eyes, but for obvious reasons supplies are limited. This shortage has stimulated research into the best methods of preserving and storing donor eyes in order to eliminate any preventable factors which may be responsible for loss or wastage of this precious material.

Although it is not a universal practice, in this Corneo-Plastic Unit, no donor eye is used unless contamination by pathogenic bacteria has been absolutely excluded. During the period January, 1955, to June, 1956, 51 (41·3 per cent.) out of 138 *post-mortem* eyes, donated to this Bank for corneal grafting and stored in sterile liquid paraffin, were found on culture to be contaminated and unsuitable for use. The organisms isolated belonged to the staphylococcal, coliform, proteus, and corynebacterium groups. Contamination with a penicillin-sensitive strain of *Staphylococcus albus* is not regarded as a bar to the use of an eye for corneal grafting.

The high incidence of wastage through bacterial contamination in addition to the general shortage caused concern and prompted an investigation to find a more suitable storage medium than sterile liquid paraffin. The use of antibiotics was explored, but it was found that immersion of an enucleated eye for a short period in an antibiotic solution would not necessarily guarantee sterility. Moreover, on account of the high proportion of resistant bacteria, the use of penicillin was abandoned as unsafe. A combination of chloramphenicol and streptomycin has been found to give the most consistently satisfactory results when used in concentrations of 1,000 μg. per ml., but even then it is essential for the eye to be in contact with the antibiotics for at least 48 hours. This is presumably due to the time required for the antibiotics to penetrate to the deeper structures of the eye.

The criteria for the physiological requirements of corneal storage described by Davson (1955) formed the basis of the investigation which has resulted in the development of a new medium. After being stored for 14 days in

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this medium, eyes were histologically in a better condition than those stored in liquid paraffin, and the structures of the eye showed less degenerative changes. Corneae taken from eyes stored in the new medium have now been used in 26 cases, and the clinical results have been satisfactory. Also at operation it was found that the eyes were more easily handled and washed than those stored in liquid paraffin. Further, a possible source of failure of grafting due to contamination of the wound by liquid paraffin has been eliminated. For these reasons it has been decided that sterile liquid paraffin will be replaced by the new medium in this Eye Bank.

Procedure

The following procedure is now routine. Containers filled with the new medium are either issued by the laboratory to the Eye Bank or despatched direct to hospitals in small insulated ice-boxes for the use of colleagues who procure donor eyes in different parts of the country. The stocks of medium in hospitals are maintained and replaced as required.

Donor eyes are removed either by the medical staff of this Unit when they collect, or by colleagues who obtain the material on their behalf. As soon as possible after removal the eye is placed in the medium, and then despatched in the small ice-box to the Eye Bank. The eye is thus subjected to the sterilizing action of the medium during transit. On arrival at the Eye Bank it is stored at refrigerator or deep-freeze temperature until required for use. If there is any change in colour of the indicator from red to orange or yellow, or if the medium appears suspiciously turbid, the eye is immediately removed, cultured, and transferred to a fresh container of medium.

Further investigation is required to determine by tissue culture and other methods whether this new medium increases the longevity of the cornea beyond the accepted 10-day period when stored in other types of medium.

Apparatus and Material required for Preparing the New Medium

(1) The standard blood-transfusion bottle graduated in 100-ml. quantities, and fitted with a screw-cap and rubber liner, is the most suitable and convenient type of container for preparing bulk quantities of the medium.

(2) For the storage of eyes, wide-mouth specimen jars of 2-oz. fitted with an aluminium screw-cap and wax liner are used (these are issued by the Supply Branch of the Ministry of Health).

(3) A rubber bung to fit the blood transfusion bottle is fitted with an air inlet containing a cotton-wool filter, and a piece of glass tubing bent at an angle of 90°. The bung is sterilized separately and fitted to the bottle before the jars are filled.

Ingredients of Medium

(*a*) Intradex (6 per cent. dextran in normal saline) (Glaxo)
(*b*) Dextrose 5 per cent. sterile solution in distilled water

(*c*) Phenol red sterile solution 1:1,000

(*d*) Chloramphenicol

(*e*) Streptomycin

(*f*) Standard nutrient agar (issued by the Southern Group Laboratory). This is melted in a steamer before use.

It is essential that the chemical constituents of any medium should be as nearly as possible in equilibrium with those of the aqueous humour and the tears which bathe the posterior and anterior surfaces of the cornea for the purpose of viability and nourishment and to maintain the hydration of the cornea. It is also essential to prevent any osmotic alteration in the volume of the globe. In practice, however, it has been found that a slightly hypertonic solution is preferable, as this prevents the cornea from imbibing fluid and becoming oedematous. The eye does lose some volume, but it is considered that the slight hypertonicity is justified in that it prevents excessive hydration of the cornea which favours disintegration of the supporting protein scaffold of the cells and autolysis of the protein.

Dextran in solution is selected on account of the size of its molecules and its properties as a plasma expander to maintain equilibrium with the intra-ocular proteins of the aqueous humour and the vitreous body.

The isotonic solution of dextrose is used both to maintain equilibrium with the diffusible ions and molecules in the aqueous and vitreous body and to provide nourishment for the cornea.

The phenol red indicator is added to enable the pH to be checked and to detect contamination. When bacteria are present, the indicator changes from red→orange→yellow. It has been found that a change in pH does occur after 14 days' storage, but the medium has been proved to be sterile after culture; it is believed that this change in colour is indicative of metabolism of the dextrose by the eye during storage.

Nutrient agar (to a concentration of 0·32 per cent. agar) is used to increase the viscosity of the medium and to act as a vehicle and buffer to protect the cornea during transit and storage.

The 15 ml. nutrient agar added to each container is to economize in the amount of medium required and also to provide a cushion for the eye at the bottom of the container.

Preparation of Medium

The medium is prepared in 500-ml. quantities (this being sufficient to fill fourteen or fifteen jars). The ingredients are added to a sterile bottle in the following order:

Intradex	200 ml.
Dextrose solution . . .	200 ml.
Phenol red solution . . .	20 ml.
Chloramphenicol . . .	0·5 gm.
Streptomycin	0·5 gm.
Melted nutrient agar . .	80 ml.

The bottle is well shaken to ensure thorough mixing of the contents; it is sterilized at 20 lb. pressure for 30 minutes and then cooled to 60° C. before the jars are filled. After sterilization the pH is 7·4 to 7·6. Owing to its viscosity it is essential that the medium be kept at a temperature of 60° C. when filling the jars.

Summary

(1) A new medium for the storage of *post-mortem* donor eyes for corneal grafting is described.

(2) The high rate of potential infection (41 per cent.) of *post-mortem* donor eyes has been greatly diminished and the wastage of eyes has been reduced.

(3) The method has been proved to be valuable in practice. The medium is simple to prepare, avoids oil contamination of the graft, and ensures sterility which can be seen at a glance. Delay for culture report is thus eliminated.

(4) The medium also helps to nourish the graft during storage.

(5) Further research is required to determine whether storage in the new medium increases the optimum period during which an eye may be stored.

I wish to acknowledge the help and encouragement I have received from Mr. B. W. Rycroft and his assistants Mr. G. Romanes and Dr. M. Garber during the investigations.

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RETROPOSITION OF THE CONJUNCTIVA

A NEW APPROACH TO TRACHOMATOUS ENTROPION*

BY

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THE results of tarsectomy following trachoma are often unsatisfactory. The shrunken conjunctiva pulls the lid margin of the upper lid in, and tends to produce lagophthalmos. The greatest danger of ill-performed tarsectomy is the production of xerosis of the conjunctiva following damage to the ducts of the lacrimal gland. Cosmetically, the skin, deprived of its support, overhangs the lashes (*Fig. 1, right eyes*).

Right Left

FIG. 1.—Effect of surgery in two cases. Tarsectomy of the right upper lids and retroposition of conjunctiva of left upper lids.
Note blepharochalasis-like aspect of right upper lids.

These complications follow retraction of the conjunctival flap and we aimed at fixing the flap in its retracted position (forming the tarsal fold at the same time) and coating the uncovered inner lid surface by a mucous membrane graft.

Technique

After 0·1 ml. 4 per cent. Novocain with adrenaline has been injected into the lid margin, the lid is everted with the aid of three bridle sutures over a spatula. The same solution is injected under pressure through a 20-gauge cannula introduced temporally and advanced superficially beneath the conjunctiva, so that the lid becomes swollen and separated from its support. With a keratome, held per-

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pendicularly to the plane of the marginal lid strip, a section is made through the tarsus at the marginal borderline of the sulcus subtarsalis. The knife is introduced at the temporal end of this section and slid along the convex margin of the tarsal plate to counterpuncture the nasal end. The swollen conjunctiva is separated from its support (Fig. 2). Undermining beyond the tarsal plate should be avoided and no scars should be produced in the vicinity of the lacrimal glands. Thereafter the tarsal plate (and scars in the case of re-operation after tarsectomy) is completely removed. Three double-armed silk sutures are evenly distributed over the cut margin of the flap and, after the flap has retracted, the stitches pierce the skin at the line of the tarsal fold. These stitches fix the retracted flap, leaving an area uncovered (Fig. 3) to be coated with a mucous membrane graft which is taken from the lip.

FIG. 2.—Slicing of conjunctival flap.

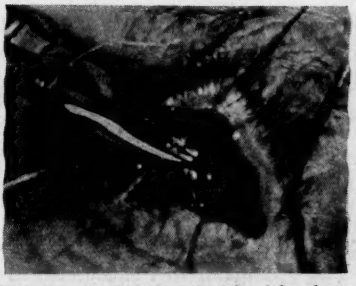

FIG. 3.—Conjunctival flap fixed by three stitches through the skin in its retracted position, leaving part of the inner surface uncovered.

The graft is laid on the uncovered area of the lid and stitched with the second needles of the double-armed sutures. The sutures are tied over rubber on the skin, folding the skin and joining the conjunctival flap and the graft in the depth of the fornix. Three double-armed sutures are placed in the lower margin of the graft and the needles are directed towards the lashes through the gap between the skin and the tarsal strip (Fig. 4). The sutures are tied on the margin over rubber (Fig. 5).

FIG. 4.—Free edge of graft pulled by sutures to the margin.

FIG. 5.—Appearance after tying last sutures.

The bridle-sutures are discarded and a bandage applied. The sutures are removed on the sixth day. The procedure may be performed in the same way on

the lower lid. When carried out simultaneously on both lids the operation does not take more than 25 minutes.

Results

The operation described was performed on thirty cases (Table).

TABLE
PARTICULARS OF THIRTY OPERATIONS

Lid		Operation			Retroposition		Entropion	
Upper	Lower	First	Second	Third	Total	Partial	Tracho-matous	Non-tracho-matous
21	9	16	9	5	27	3	27	3

Though designed originally for the upper lid, it proved to be the method of choice for the relief of cicatricial entropion of the lower lid as well. It was performed with complete success in three cases where the marginal plastic procedure of van Millingen failed; the restoration of the normal lower fornix, the hidden position of the graft, and its prevention from desiccation are further advantages of the new procedure.

The operation was successful in 29 out of thirty cases. In four eyes the upper and lower lids were grafted. The smooth inner surface of the lids is said to be comfortable and xerosis and pannus are cleared.

Discussion

The favourable effects of mucous grafts are mechanical and biological. In the late stages of trachoma, the fornices shrink and consequently fail to act as reservoirs for tears. This procedure restores these physiological reservoirs, as measured by a 2 to 3-fold dilution of instilled fluorescein (Nover and Jaeger, 1952). The causative agents of trachoma are presumed (Poleff, 1951) to infect the epithelial cells of the graft and to enhance the formation of antibodies by multiplying. At the same time, they lose their pathogenicity. No inclusion bodies, however, were found in one of our transplants.

Summary

In thirty cases of cicatricial—mostly trachomatous—entropion of the upper or lower lids, a new type of operation was performed; after tarsectomy and/or extirpation of scars, the tarsal conjunctiva was allowed to retract and was then fixed in the depth of the fornix; the uncovered inner surface of the lid was coated with a mucous membrane graft. The favourable effects are due partly to mechanical factors and partly to the biological effects of the graft.

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CHLORPROMAZINE IN OCULAR SURGERY*

BY

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IN INDIA cataract surgery is a major problem. We consider any person above 60 years of age as a potential cataract patient if he is not one already. Through lack of education, the cooperation of the patient in intra-ocular surgery is not all one would like it to be, and it is therefore best not to rely on the patient's cooperation but to administer suitable sedatives.

Chlorpromazine promises to be a highly suitable drug for this purpose. Delay and Deniker (1955) described its central depressant properties, and Decourt (1953) pointed out its hypnotic and anti-emetic effects, suggesting that analgesics and local anaesthetics have a more lasting effect when chlorpromazine has been used for general sedation. Moore (1955) considered it to be a satisfactory premedication for ocular surgery and stated that it eliminated the risk of non-cooperation on the part of the patient; he used barbiturate premedication together with chlorpromazine 3 days before operation. Burn, Hopkin, Edward, and Jones (1955), who tried chlorpromazine in combination with promezathine and pethidine, stated that this ensured muscular relaxation and freedom from apprehension, with minimal bleeding during operation. Rycroft and Romanes (1955) were of a similar opinion. Pierse and Ives (1955), however, thought that chlorpromazine had a local emetic action which was distinct from its central anti-emetic effect, and therefore advised that it should not be administered orally; they found the effects of the drug to be unpredictable and suggested that it should only be used by an expert anaesthetist.

Material and Methods

105 cases of intra-ocular operation which were admitted to the wards of the S.N. Hospital, Agra, form the subject of this study. Ten were patients in whom iridencleisis was performed, and the other 95 were cases of intra-capsular cataract extraction. No selection of cases was made.

Nembutal 0·75 gr. was given to each patient one hour before the operation, followed by 50 mg. chlorpromazine (Largactil) intramuscularly 30 minutes before the operation.

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The operation was performed under 2 per cent. anethaine local surface anaesthesia. A facial block and a retrobulbar injection of 2 per cent. Novocain were given in each case. The belly of the superior rectus muscle was not injected.

The patients were all between 40 and 65 years of age (average 55). Sixty were males and 45 were females. The blood pressure before the administration of chlorpromazine and before the operation is shown in Table I.

TABLE I
FALL IN BLOOD PRESSURE IN CASES GIVEN CHLORPROMAZINE

No. of Cases	Blood Pressure (mm. Hg)							
	Systolic				Diastolic			
	No. showing Fall of 5 mm. or More	Maximum	Average	Minimum	No. showing Fall of 5 mm. or More	Maximum	Average	Minimum
105	90	46	12·73	5	57	30	11·04	5

The intra-ocular pressure before the administration of the drug and before the retrobulbar injection is shown in Table II.

TABLE II
VARIATIONS IN INTRA-OCULAR PRESSURE

No. of Cases	No. showing No Change in Pressure	Intra-Ocular Pressure (mm. Hg)							
		Fall				Rise			
		No.	Minimum	Average	Maximum	No.	Minimum	Average	Maximum
105	25	74	2	7·3	48	6	5	11·7	20

The mental state and general behaviour of the patient at the time of operation is shown in Table III.

TABLE III
GENERAL CO-OPERATION OF THE PATIENT (PER CENT.)

Author	Date	Excellent	Good	Uncooperative	Total
Moore	1955	60	40	0	100
This Series... ...	1957	56	44	0	100

Congestion of the eyeball, haemorrhage during the operation, vitreous prolapse, and reactions to painful stimuli are shown in Table IV (opposite).

TABLE IV
COMPLICATIONS DURING OR AFTER OPERATION

Type of Medication	No. of Cases	Complication			
		Vitreous Prolapse	Iris Prolapse	Hyphaema	None
No Drug	100	10	4	20	66
Chlorpromazine ...	95	5	4	60	26
Curare	100	0	Not noted	Not noted	—

Results

In general, the patients were relaxed and free from mental tension or apprehension, though the muscular relaxation was less satisfactory than that obtained by curare or curare-like products. The patients could respond to questions, and they reacted to painful stimuli, as was evident at the time of giving the facial block and retrobulbar injections. Pain was specially evident at the insertion of the superior rectus stitch, but the reaction lasted only as long as the stimulus was maintained. The patients protested by wincing and by irregular movements of the eyeball.

The patients complained of a shivering sensation due to the coldness of the skin, but there was no obvious pallor of the face and lips. The eyes looked rather congested, and a greater degree of haemorrhage occurred during the operation than when Nembutal sedation was used alone.

The patients usually complained of dryness of the mouth about 20 minutes after the administration of the drug, and in 30 minutes or so the voice became husky. Several patients had to be given sips of water before the operation. There was no post-operative vomiting or retention of urine.

Discussion

Barbiturate sedation of patients for intra-ocular surgery has been the usual procedure in this unit. This form of sedation may give a false sense of security to the operator, as the patient often looks drowsy and sleepy, though there is no muscular relaxation and the patient's anxiety and tension are not allayed. This sedation does not reduce the patient's reaction to painful stimuli which lasts not only while the stimulus is applied but far beyond it. The combination of barbiturates with chlorpromazine, as used by Moore (1955), has helped to produce a calmer, more cooperative, and more relaxed patient. Burn and others (1955) found this to be the case when they administered chlorpromazine in combination with promezathine and pethidine.

In the present series it has been observed that this drug does not provide such complete muscular relaxation as curare or curare-like products, but

that mental apprehension, tenseness, and anxiety are almost completely eliminated. The patient is generally calmer and more cooperative, and can obey commands given to him. Much stress is usually laid on the need for the patient's cooperation during the operation, but we do not rely on this. Our aim in cataract surgery is to render the cooperation of the patient unnecessary and to regulate his behaviour so as to preclude the blame of a bad result being laid on his shoulders. Curare and curare-like products provide complete muscular relaxation, but chlorpromazine provides in addition complete mental relaxation and produces a carefree attitude in the patients. A combination of curare with chlorpromazine seems to be a rational procedure.

Decourt (1953) believed that chlorpromazine enhanced the effect of local anaesthetics, but we have not found this to be so. On the contrary, we feel that larger quantities of local anaesthetics are required to produce the same effects, and we have noted that the reaction to painful stimuli was often more marked than is usually seen under simple barbiturate sedation (1·5 gr.). In cataract and glaucoma operations, Burn and others (1955) found that the conditions produced were excellent, but in their six cases of acute glaucoma involuntary movements of the eyeball limited the usefulness of this drug. In our five similar cases we did not find reaction to painful stimuli to be of any consequence. All these cases could be successfully operated upon under local anaesthesia.

The hypotensive effects of the drug, at least by the intramuscular route and in the doses employed by us, do not seem to be of any magnitude in persons not already hypertensive. About 14 per cent. of our cases showed no fall in systolic pressure, and in the rest there was an average fall of only 12 mm. Hg. The response of the diastolic pressure was more equivocal and 45·7 per cent. of cases showed no fall in diastolic pressure, the average fall being 11·7 mm. Hg. If hypertensive cases are excluded, the fall is less significant. There was no tachycardia or severe hypotension to cause any anxiety, and the fears expressed by other authors about these two complications are not shared by us. We do not think that the effects of the drug call for any particular caution or for the services of an expert anaesthetist. The intramuscular injection of the drug is quite adequate and safe.

Paul and Leopold (1956), in an experimental study on cats and rabbits, found a positive fall in intra-ocular pressure. Burn and others (1955) noted the same in the case of human beings. Our own results are equivocal and do not show a uniform tendency towards a fall in intra-ocular pressure; some cases even showed a rise (5·7 per cent.), while in a considerable number no effect was seen (23·8 per cent.), and in about the same number the fall was insignificant (2 to 3 mm. Hg Schiötz). The fall in intra-ocular pressure in no way helps the operator, but a rise in intra-ocular pressure is embarrassing in cataract extractions (in two cases there was a rise of about 20 mm. Hg Schiötz).

In our cases, the eyes looked more congested and the preparation of conjunctival flaps resulted in an embarrassing degree of haemorrhage. This observation is contrary to that of Burn and others, who could complete a bloodless operation and considered this to be a definite advantage of chlorpromazine. They attributed the effects to a general fall in blood pressure. Our own observations reveal that the fall in blood pressure is not uniform and not very significant. The congestion of the eyeball is perhaps due to the adrenolytic effect of the drug which produces some degree of peripheral vasodilatation. These differences may be due to our not having used promethazine, an anti-histaminic compound which has perhaps a decongestive effect.

The drug does help to reduce the percentage of cases of vitreous prolapse, but post-operative iris prolapse is no more common with this sedation than without it.

The continued administration of the drug in the form of tablets in the post-operative period is a considerable help in the proper care of the patient. The complications which may arise in the first 2 post-operative days are largely due to non-cooperation by the patient, and these risks are eliminated by continued sedation.

The drug had no untoward effects in the dosage used, except for slight dryness of the mouth and huskiness of the voice. In a few cases the passage of urine was delayed but this, too, was of little clinical significance. Post-operative vomiting, nausea, or retching was absent, probably because the sedation was continued for 2 days post-operatively. Recovery from the effects of the drug was slow, gradual, and uneventful.

Summary

(1) In intra-ocular operations (95 for cataract and ten for iridencleisis), 0·75 gr. Nembutal and 50 mg. chlorpromazine (Largactil) were given 30 minutes before the operation.

(2) The sedative and hypotensive effects of the latter are described.

(3) Other effects of chlorpromazine are noted.

(4) Its use as a sedative in ocular surgery is discussed.

(5) Its use as a sedative in ocular surgery with curare is recommended.

(6) It is suggested that it should be combined with a drug such as promethazine to counteract its adrenolytic activity.

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CASE NOTES

MOOREN'S ULCER TREATED BY DIATHERMY COAGULATION*†

BY

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MOOREN'S ULCER is a relatively rare condition and treatment in the past has been for the most part unsatisfactory. Indeed, the multiplicity of therapeutic methods attempted or recommended in the literature is suggestive of the ineffectiveness of any of them. Duke-Elder (1938) notes the following methods of treatment: excision and cauterization by carbolic, trichloracetic acid, iodine, absolute alcohol, or other chemicals; thermo-cautery; zinc iontophoresis; radium; ultra-violet light; the production of hypotony by a sclerectomy or by repeatedly opening a corneal incision; a "delimiting keratotomy" in front of the advancing edge.

In recent times β-radiation has been used, notably by Lederman (1957), who gave 1,000 r once a week for four treatments. The results in 45 eyes were fifteen cured, sixteen failed, and fourteen improved, so that a really successful outcome was achieved in only about 30 per cent. of cases.

Treatment by diathermy coagulation does not appear to have been given an adequate trial. Text-books on ophthalmic surgery by Spaeth (1948), Philps (1950), Stallard (1950), and Arruga (1952) do not mention this method. One case treated successfully by diathermy coagulation was recorded by Malmquist (1947). The details of a further case are given below.

Case Report

An agricultural peasant, aged 25 years, stated that he had had a watery, painful, and slightly red eye for the past 3 months. He thought that the condition was the result of being flicked in the eye by a cow's tail.

Examination (November 21, 1955) revealed a typical Mooren's ulcer in the right eye (Fig. 1, opposite) extending from the limbus in a more or less straight line joining 12 to 3.30 o'clock. The advancing border had undermined the anterior third of the depth of the cornea, and formed a grey overhanging edge which is so characteristic. The advancing edge stained faintly with fluorescein while the more peripheral area between the edge and the limbus had healed over with the formation of scar tissue and some slight vascularization. The rest of the cornea was clear and visual acuity was 6/6. There was some ciliary congestion localized to the area of the ulcer. The lens and fundus were normal. The other eye was normal.

Therapy.—Atropine ointment thrice daily was prescribed and a pad applied for 10 days with no improvement.

* The case was shown at a clinical meeting of the Bengal Ophthalmological Society on January 31, 1957.
† Date received for publication March 29, 1957.

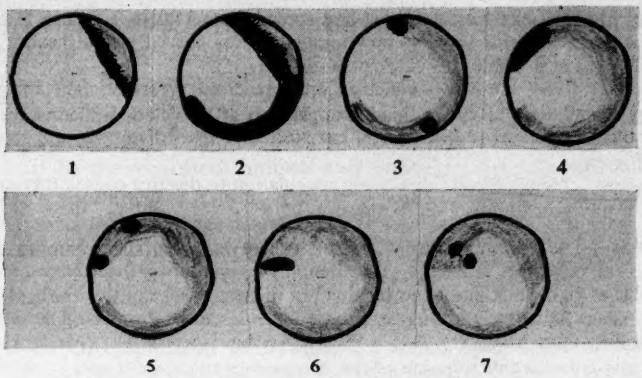

FIG. 1.—Condition, November 21, 1955.
FIG. 2.—After β rays, January–March, 1956.
FIG. 3.—After first diathermy, March 22, 1956.
FIG. 4.—After second diathermy, April 26, 1956.
FIG. 5.—After third diathermy, May 31, 1956.
FIG. 6.—After fourth diathermy, June 27, 1956.
FIG. 7.—After fifth diathermy, August 2, 1956.

On December 2, 1955, a partial-thickness delimiting keratotomy with cauterization of the ulcer with pure carbolic acid was performed but without beneficial result.

Two weeks later, the ulcer was again cauterized with carbolic acid but without benefit.

A course of β-rays was next given through the courtesy of Dr Nirmal Ghose at the Eye Infirmary, Medical College Hospital, Calcutta. Applications were given twice weekly for 8 weeks and 400 r.e.p. were given at each sitting. At first there appeared to be some regression and healing, but soon after the completion of the treatment the ulcer had extended round the limbus from 12 to 11 o'clock above and from 3.30 to 8 o'clock below (Fig. 2). The eye was still painful, watery, and slightly congested.

On March 22, 1956, under local anaesthesia with cocaine 4 per cent. drops and a sub-tenon injection of xylocaine 1 per cent., the whole of the advancing edge of the ulcer was cauterized by diathermy-coagulation. The Moorfields diathermy machine was used with the blunt Larsson electrode. About three-quarters of the current usually required for non-penetrating diathermy coagulation through the sclera in detachment work appeared satisfactory. The electrode was applied very lightly to the ulcer and the clear cornea just in front of the advancing edge. The coagulated area could be seen to turn a whitish colour. The electrode was kept in contact with each area for about 2 seconds. Great care was taken to apply the electrode with only very light pressure, so as to confine the coagulative process to the anterior half of the thickness of the cornea and so to avoid penetration.

The eye was kept covered and atropine applied twice daily, and one week later the ulcer had healed except at two places at 11.0 and 5 o'clock near the limbus (Fig. 3). Scarring was satisfactory and there was practically no vascularization.

On April 26, 1926, the two unhealed areas were much the same and further similar diathermy coagulation was applied. The area at 11 o'clock failed to heal. This area persisted and the cornea appeared so thin at this point that further treatment was deliberately withheld.

By May 31, 1956, the ulcerated area had spread from 11.0 to 9 o'clock (Fig. 4), and further diathermy coagulation was now applied. This caused partial healing, but two very small areas at 9·0 and 11 o'clock persisted (Fig. 5).

On June 27, 1956, these two unhealed areas received a further light application of diathermy coagulation, and after this the upper area at 11 o'clock healed while the lower one at 9 o'clock not only failed to heal but started to extend towards the centre of the cornea (Fig. 6).

On August 2, 1956, a further diathermy coagulation to the area caused this last remaining part of the ulcer to heal after 12 days.

Follow-up.—The patient returned to his village but returned a month later with recurrence of pain and watering. Examination revealed two fresh ulcers, one on the former scar at 10 o'clock and one near this but in clear cornea nearer the centre (Fig. 7). On September 20, 1956, these areas received further diathermy coagulation, and this caused healing after 3 weeks.

There was considerable thinning of the cornea over the scarred area of former ulceration and diathermy coagulation. One area at 10 o'clock was particularly thin—so thin that ectasia was expected. (Figs 8 and 9.)

FIG. 8. — Slit-lamp appearance of thin area.

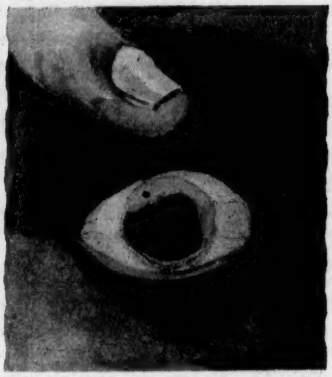

FIG. 9.—Thin area at the 10 o'clock meridian looking like a small hole in the corneal scar.

No further ulceration occurred, however, and 3½ months later, January 31, 1957, the scars had considerably faded and the thin areas were now of almost normal thickness. What was surprising was that the extremely thin area seen in Fig. 9 had almost disappeared. Visual acuity with −1 D sph. and −1 D cyl., axis 45°, was 6/12 ptly.

Comment

Although the patient was only 25 years old, the ulcer was absolutely typical of a Mooren's ulcer, so that no other diagnosis was possible. It was quite unlike marginal keratitis or marginal ectatic dystrophy.

Cauterization with carbolic acid was ineffective, probably because this only gives destruction of the most superficial surface cells. β-rays seemed in this case only to irritate the ulcer and cause it to spread rapidly. Great

credit goes to the patient, a simple country lad, for his fortitude in persisting with treatment lasting about 8½ months. More drastic or more frequent coagulation was not attempted for fear of doing irreparable damage to the cornea with danger of the loss of the eye.

A great advantage of this method of diathermy coagulation is that the surgeon can do the treatment himself and modify it to each particular case. Diathermy coagulation is available in most hospitals and there is no fear of radiation burns to the surgeon or his assistants.

Summary

A case of Mooren's ulcer failed to respond to chemical cauterization. β-ray applications appeared to irritate the lesion and cause it to spread. Diathermy coagulation with the blunt Larsson electrode caused rapid healing except for some outlying areas which needed five further coagulations before the ulcer ceased spreading and finally healed. The advantages of this technique are noted.

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INTRA-OCULAR FRAGMENT OF ALUMINIUM ALLOY TOLERATED FOR 12 YEARS*

BY

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DETAILS of this patient are reported since it is so rarely possible to observe the condition of an eye which has retained an aluminium foreign body for a number of years.

Case Report

A man aged 21 in July, 1944, was riding in a truck which exploded a German mine. His body, especially his face and eyes, was peppered with small fragments of metal. Examination at that time showed a number of lacerations of the face and body, and an opacity in the right lens.

At the base hospital localization by ring *x*-ray showed large numbers of foreign bodies in the soft tissue of the face. A dense foreign body lay in the right orbit above and behind the globe: one other of low radio density was seen within the ring in the antero-posterior view.

In August, 1944, a curette evacuation was performed on the right lens, followed 2 months later by a capsulotomy. Post-operatively vision in the right eye could be improved to 6/9.

In April, 1945, it was noted that the right retina showed large areas of destruction and heavy pigmentation, and the vision was not improved beyond counting fingers.

Examination.—The patient had no further trouble until February, 1956, when he was seen at King's College Hospital out-patient clinic complaining that his right eye had been sore for one day. He was found to have a corneal abrasion, and slit-lamp examination showed a deep anterior chamber, with a herniation of the vitreous through an aperture in the lens capsule; no flare or cells were seen. A mobile brown-coloured foreign body was noted in the inferior angle of the anterior chamber. The iris behind the foreign body was atrophic and had a whitish colour suggesting an "imprint" in the iris (see Figure). Pigmentary changes in the retina could be seen through a very turbid vitreous. An *x*-ray showed numerous opaque foreign bodies in the orbital soft tissues, but the foreign body in the globe did not show.

Treatment.—After the abrasion had healed, on March 29, 1956, the foreign body was removed through a keratome incision, a Meibomian curette being used to lift the fragment out of the anterior chamber. Analysis of the foreign body showed it to be a fragmented mass, partly organic. The residue after incineration gave positive tests for aluminium, with possible traces of iron and magnesium.

Follow-up.—Post-operatively there were no immediate complications, but in April, 1956, a bullous keratitis developed which necessitated a lamellar keratoplasty. Since this operation on June 7, 1956, the patient has had no further trouble; the eye remains white and the graft clear, but the vision cannot be improved beyond 3/60.

* Received for publication January 24, 1957.

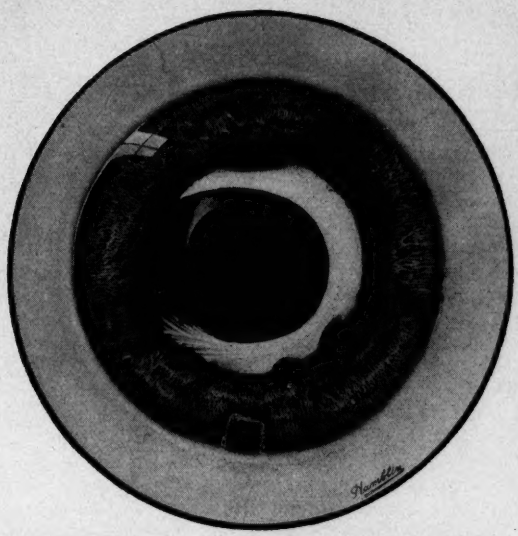

FIGURE.—Appearance of right eye on March 28, 1956. A thick lens capsule can be noted with a large central aperture through which vitreous herniates. The foreign body can be seen in the inferior angle of the anterior chamber as a brown mass surrounded by a grey imprint in the iris stroma.

Discussion

Savin (1947) showed, by animal experiments on rabbits and observations on two patients, that fragments of aluminium and its alloys, inserted into eyes, became coated with fibrin, and that the metal gradually became fragmented. Local imprints were seen where the metal came into contact with ocular tissues (e.g. the iris) as the result of local necrosis. Lens opacities were commonly seen and a quiet uveitis was present in half the experiments. Pathological fundus pigmentation occurred in many cases. His conclusion was that the eye is by no means inert to aluminium or its alloys.

The case history recorded above showed similar changes in a human eye after an aluminium alloy foreign body had been present for 12 years.

I wish to thank the Chief Medical Officer, Ministry of Pensions and National Insurance, Blackpool, for assistance and for his permission to publish details of this patient's injuries, also Dr. Harold Toms who kindly performed the analysis, and Mr. L. H. Savin under whose care the patient was admitted to hospital.

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BOOK REVIEW

The Eye in General Practice. By C. R. S. Jackson. 1957. Pp. 152, 25 figs (21 col.). Livingstone, Edinburgh and London. (21*s.*)

The author of this work has included Oxford and Edinburgh in his academic training, and so one expects to find in his book evidence of thoughtful care in observation and exposition, as is indeed the case.

In writing a book for the guidance of the general practitioner, the ophthalmologist must choose between two objectives; either spot-lighting those conditions wherein the general practitioner's initial action is crucial, as notoriously in congestive glaucoma, or presenting a meticulous but balanced survey of the subject as a whole. The author has chosen the latter objective, indicating as he says "the ways in which dangerous disease of the eye may be recognized", and guiding the general practitioner in his eternal duty of interpreting to the patient the specialist's report and advice.

Part I is concerned with the eye itself and its diseases, and with the objective of the book in mind, it would perhaps have been as well to warn the reader of the depth of the upper conjunctival fornix and its knack of hiding even large foreign bodies, and in Chapter IV on "The Watery Eye" there is no mention of the lash impacted in the punctum. These are very small points, and the diseases of the conjunctiva and the problems of epiphora are comprehensively dealt with. The cornea and its diseases are well described. Fig. 11 illustrates hypopyon ulcer, and, although the coloured illustrations are well reproduced, the essentials of the condition are not revealed in Fig. 11, nor do Figs 12 and 16 give an adequate picture of dendritic ulcer and penetrating corneal ulcer respectively. The difficult subject of intra-ocular inflammation is well described in Chapter VI, and the aims in investigation and treatment outlined. Non-vascular diseases of the retina are treated separately, Fig. 19 showing detachment is a perfect illustration, refusing to encourage the reader to expect to see something like a papal flag flying in the breeze. The other retinal diseases are described under cardio-vascular, endocrine, and metabolic disease. I find no mention of colour vision, probably wisely omitted.

Trauma is treated in Chapter XII, and a brief chapter on ametropia includes a useful page on contact lenses. Chapter X describes neatly, briefly, and clearly the problems of squint, both concomitant and paralytic. The pathology of glaucoma is described and its diagnosis and treatment outlined. Possibly it would have been wise to add emphasis to the gravity of the condition and the necessity of adequate treatment.

The book concludes with the social aspects of blindness, a useful list being given of the advantages to the patient of registration as a blind person. In some counties (at least in England) the branches of the Society for the Blind are active and helpful to both the general practitioner and the patient, and in such areas there would be no need to approach the Local Authority. The scope of the Supplementary Ophthalmic Service is described.

The book is a most useful addition to ophthalmological studies and covers in its 152 pages of good type and paper a wide field within self-imposed limitations.